

SUPPORTING INFORMATION

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Title: Controlling Helix Handedness in Water-Soluble Quinoline Oligoamide Foldamers

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S1 CD Studies on chiral Q_Y monomer units and compounds 8 – 11

CD spectra were recorded on a Jasco J-815 Circular Dichroism spectrometer using quartz cells of 2 mm optical path length. Scans were measured at 20 °C, over a wavelength range of 230 – 500 nm, with a response time of 0.5 s and a scanning speed of 100 nm/min. The CD data represent an average of two scans. All CD were baseline-corrected for signal contributions due to solvent (monomers: MeCN, foldamers: CHCl₃).

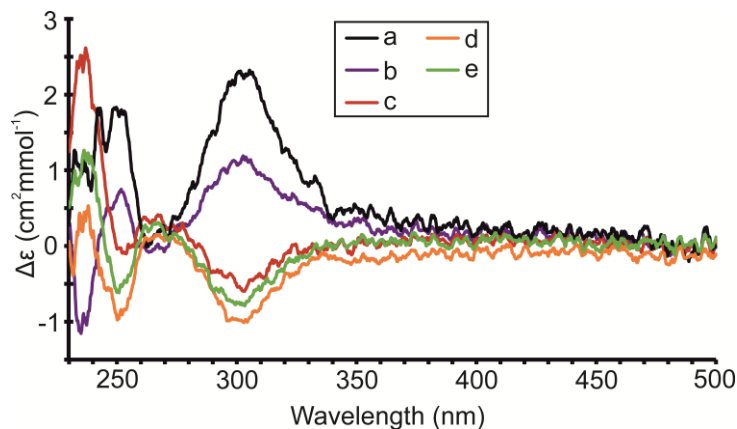


Figure S1: CD spectra of: (a) *S*-Q_{Morph} (configuration confirmed by XRD, see S4); (b) 1*S*-methyl 8-(1-(4-(2-hydroxyethyl)piperazin-1-yl)ethyl)-4-methoxy-quinoline-2-carboxylate (putative precursor to *S*-Q_{Pip}, configuration inferred from comparison with (a)); (c) 1*R*-methyl 8-(1-(4-(2-hydroxyethyl)piperazin-1-yl)ethyl)-4-methoxy-quinoline-2-carboxylate (precursor to *R*-Q_{Pip}, configuration inferred from comparison with (d)); (d) *R*-Q_{Morph} (configuration confirmed by XRD, see S4); (e) *R*-Q_{Pip} (configuration inferred from comparison with (d)).

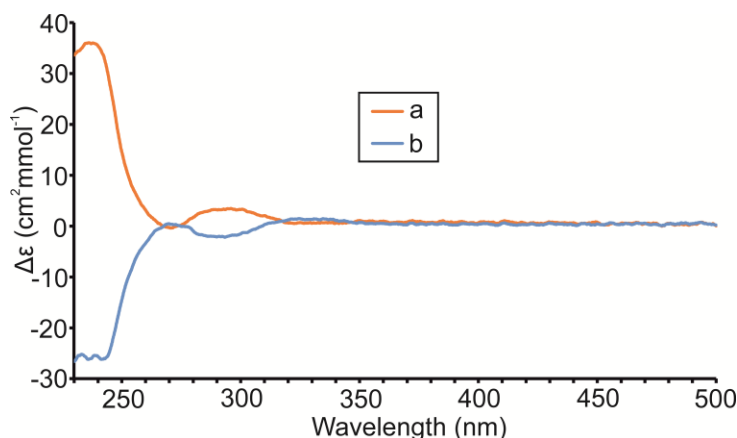


Figure S2: CD spectra of: (a) *S*-Q_{Phen}; (b) *R*-Q_{Phen}. Configurations inferred from comparison of CD sign of band at 290 – 310 nm with that of Q_{Morph} monomer.

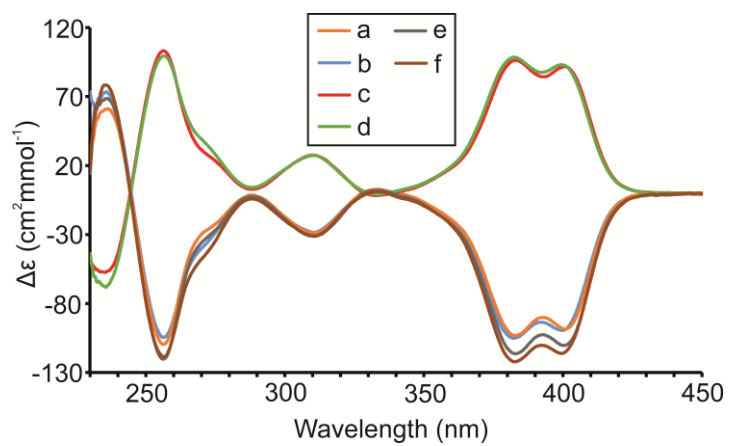


Figure S3: CD spectra of: (a) **8** free base; (b) **8** HCl salt; (c) **9** free base; (d) **9** HCl salt; (e) **10** free base; (f) **10** HCl salt.

S2 NMR stability studies on compounds 4, 8 and 11

^1H -NMR spectra were measured at 300 MHz. Chemical shifts are calibrated against residual solvent signals of CDCl_3 ($\delta = 7.26$), DMSO-d_6 ($\delta = 2.50$), MeOH-d_3 ($\delta = 3.31$), or D_2O (4.79).

Compound 4

Stability of both *P-4* and *M-4* were assessed in DMSO-d_6 at room temperature over 7 days (Figures S4 and S5 respectively).

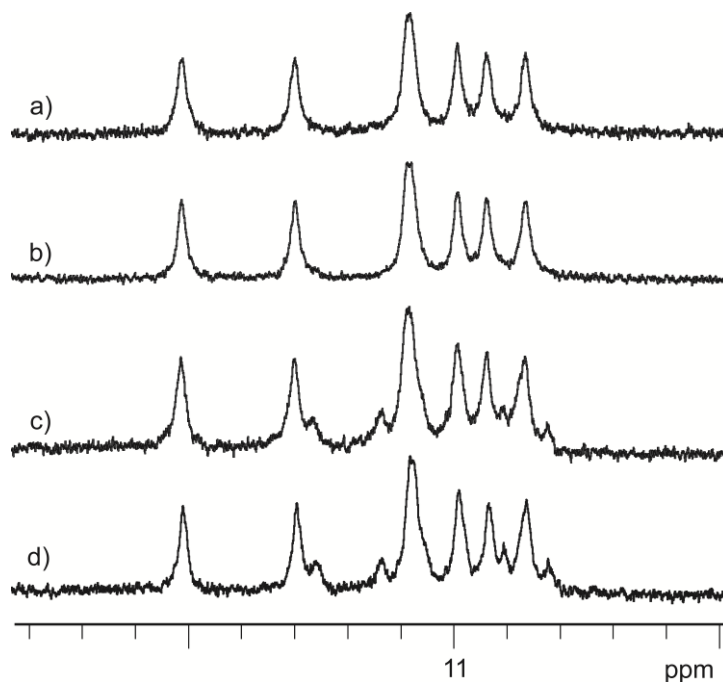


Figure S4. Carboxamide region of ^1H -NMR for *P-4* at room temperature in d_6 -DMSO at: (a) $t = 5$ min; (b) $t = 2$ h; (c) $t = 72$ h; (d) $t = 7$ days. Note equilibrated mixture consists of approximately 70% *P-4*.

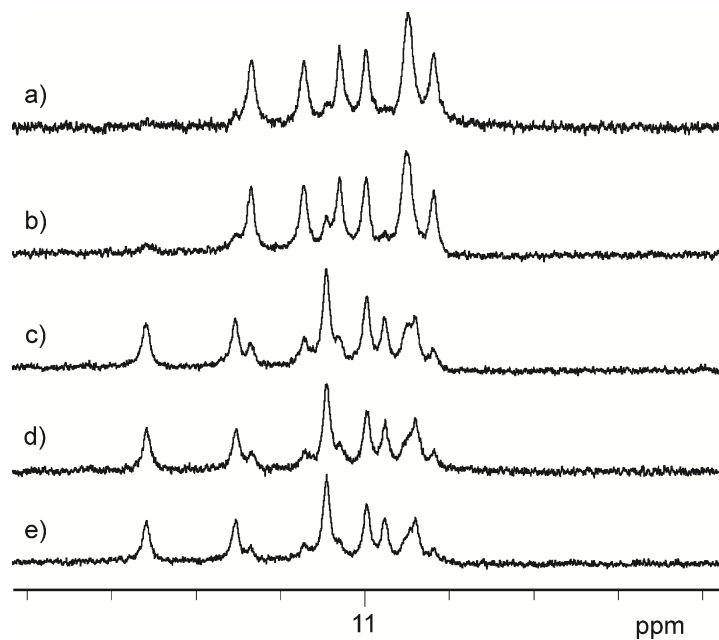


Figure S5. Carboxamide region of $^1\text{H-NMR}$ for **M-4** at room temperature in $d_6\text{-DMSO}$ at: (a) $t = 5$ min; (b) $t = 2$ h; (c) $t = 48$ h; (d) $t = 72$ h; (e) $t = 7$ days. Note equilibrated mixture consists of approximately 70% **P-4**.

Compound 8

Stability of **8** was assessed in $\text{MeCN-d}_3/\text{CDCl}_3$ (3:1) (Figure S6), MeOH-d_3 (Figure S7) and DMSO-d_6 (Figure S8) taking into account known half lives of handedness equilibration in these solvents.^[1]

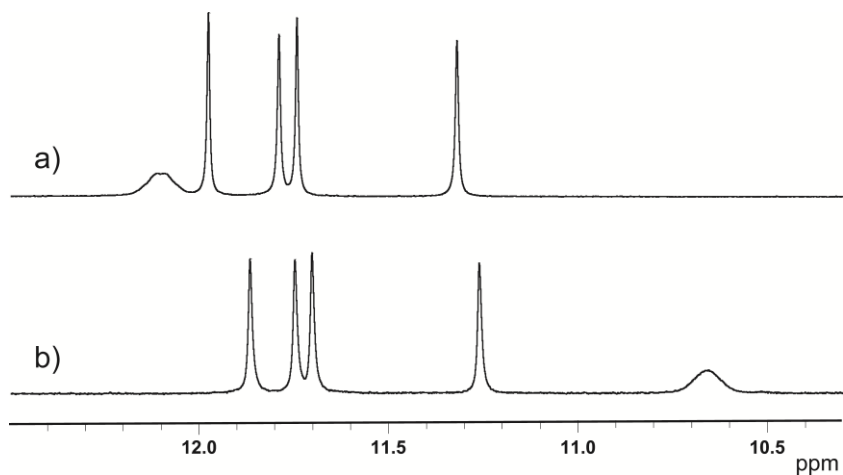


Figure S6. Carboxamide region of $^1\text{H-NMR}$ for **9** at room temperature in (a) CDCl_3 ; (b) $\text{MeCN-d}_3/\text{CDCl}_3$ (3:1) after 10 minutes.

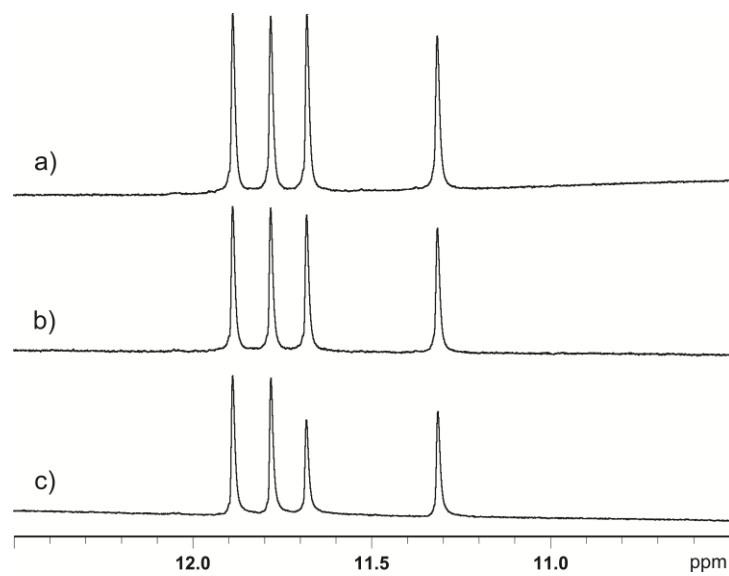


Figure S7: Carboxamide region of $^1\text{H-NMR}$ for **9** at room temperature in MeOH-d_3 at: (a) $t = 5$ min (b) $t = 2$ h; (c) $t = 20$ h.

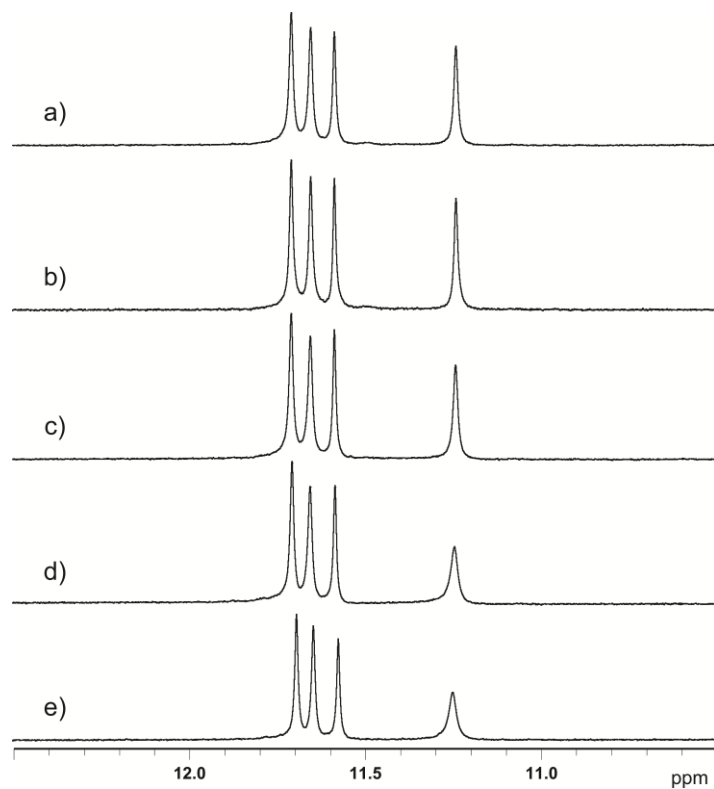


Figure S8: Carboxamide region of $^1\text{H-NMR}$ for **9** at room temperature in DMSO-d_6 at: (a) $t = 5$ min (b) $t = 5$ h; (c) $t = 48$ h; (d) $t = 14$ days; (e) $t = 4$ weeks.

Compound 11

Stability of **11** was assessed in D₂O (Figure S9).

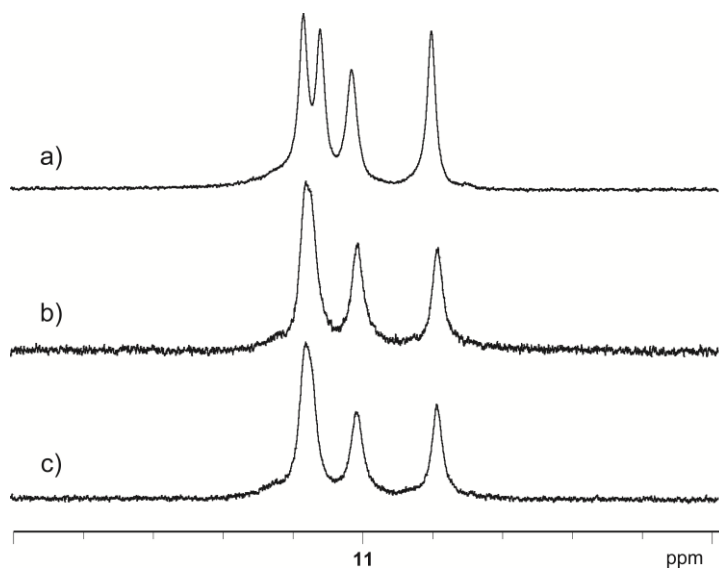


Figure S9. Carboxamide region of ¹H-NMR for **11** at: (a) $t = 5$ min at room temperature (b) $t = 15$ h at 40 °C; (c) $t = 48$ h at 40 °C.

S3 RP-HPLC stability studies on compounds 4 and 5

RP-HPLC analyses were performed at 1.5 mL min⁻¹ using a Machery-Nagel Nucleodur C18 Gravity column (4.6 x 100 mm, 3 μm). The mobile phase was composed of 0.1% (v/v) TFA-H₂O (Solvent A) and 0.1% TFA-CH₃CN (Solvent B) running the following gradients: 5–30% B over 13 min, then 30–100% B over 5 min (System A), 5–100% B over 13 min then 100% B for 5 min (System B), or 20–60% B over 25 min then 60–100% B for 5 min (System C). Monitoring by UV detection was carried out at 214 nm, 254 nm and 300 nm using a diode array detector.

Compound 4

P-4 and *M-4* were dissolved in H₂O at approximately 60 μM concentration and analyzed by RP-HPLC using System A after 30 minutes, 72 hours and 5 days at room temperature (Figures S10 – S15, showing response at 300 nm).

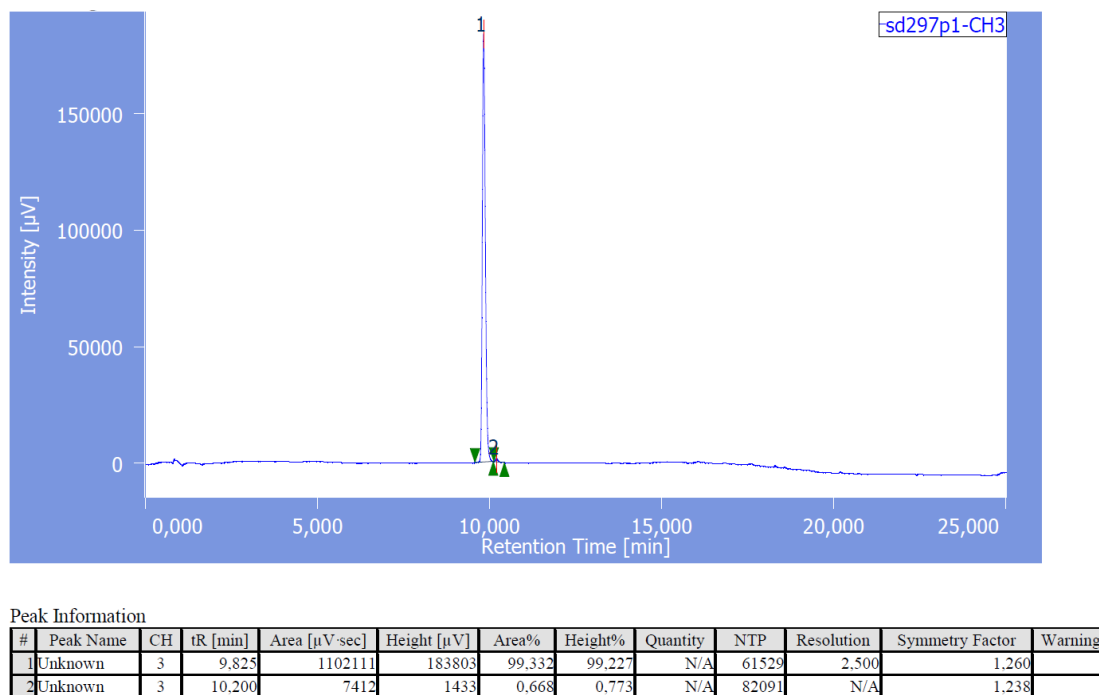
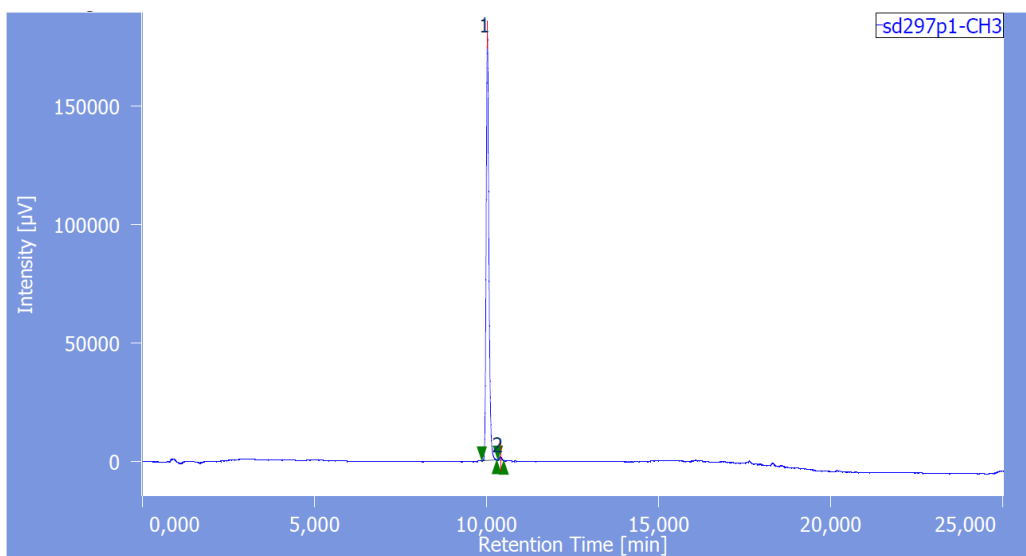


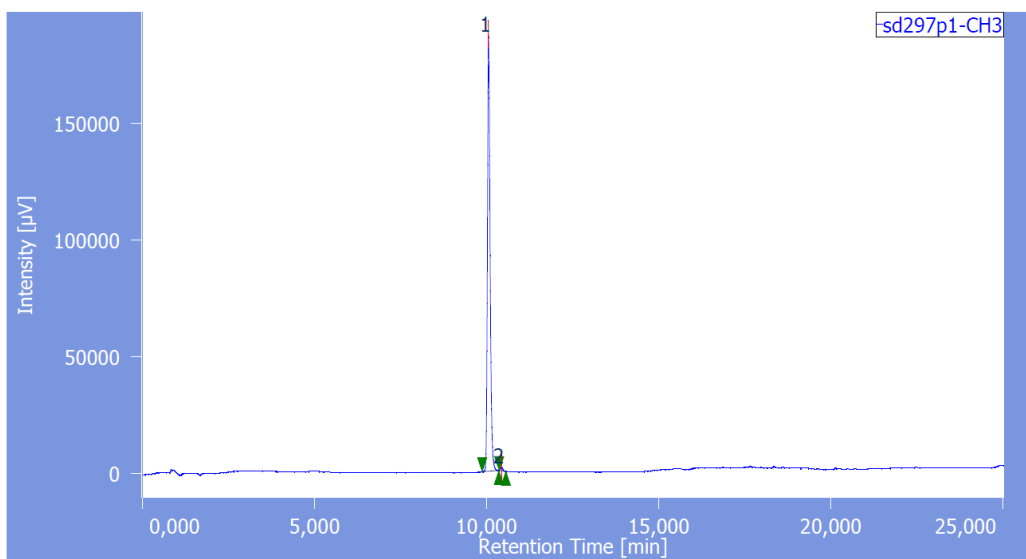
Figure S10: *P-4* after 30 min at room temperature. Product peak accounts for 99.3% of total area (98.6% de).



Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	3	10.017	1052032	179558	99.318	99.211	N/A	70958	2.653	1.314	
2	Unknown	3	10.400	7222	1428	0.682	0.789	N/A	89155	N/A	1.149	

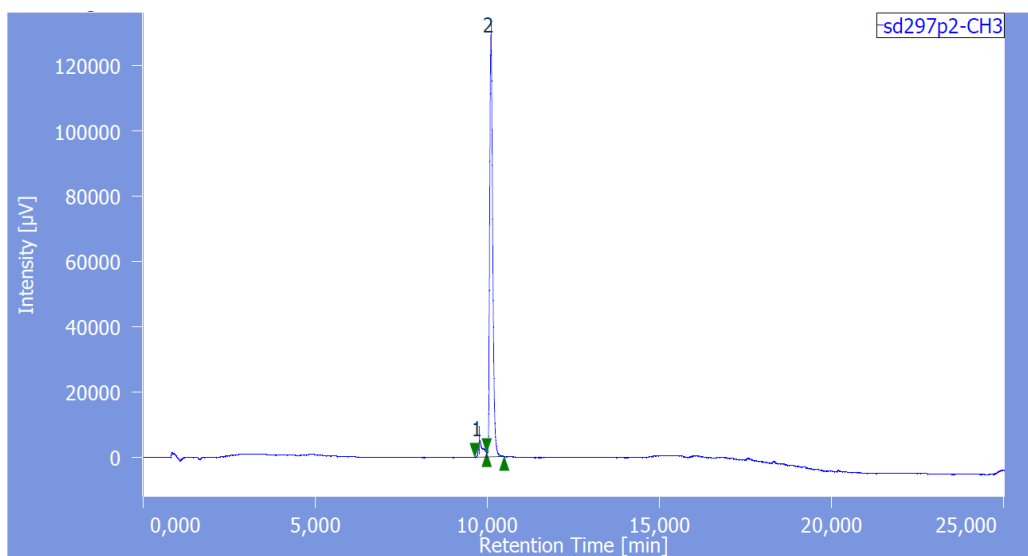
Figure S11: *P-4* after 72 h at room temperature. Product peak accounts for 99.3% of total area (98.6% de).



Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	3	10.050	1068014	187234	99.298	99.207	N/A	75285	2.672	1.324	
2	Unknown	3	10.425	7548	1496	0.702	0.793	N/A	95550	N/A	1.308	

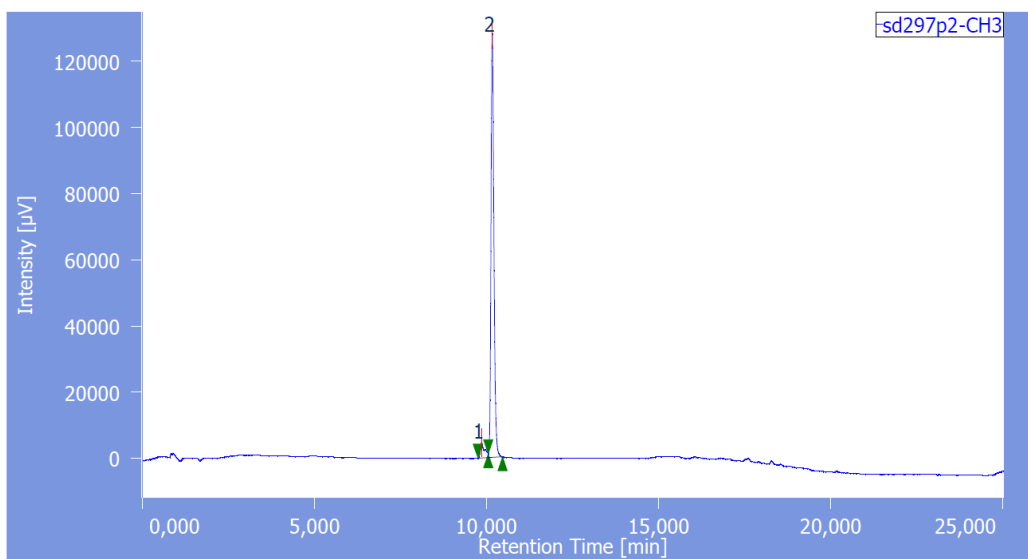
Figure S12: *P-4* after 5 days at room temperature. Product peak accounts for 99.3% of total area (98.6% de)



Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	3	9.775	45476	5113	5.430	3.804	N/A	21298	1.567	N/A	
2	Unknown	3	10.108	792021	129290	94.570	96.196	N/A	65040	N/A	1.245	

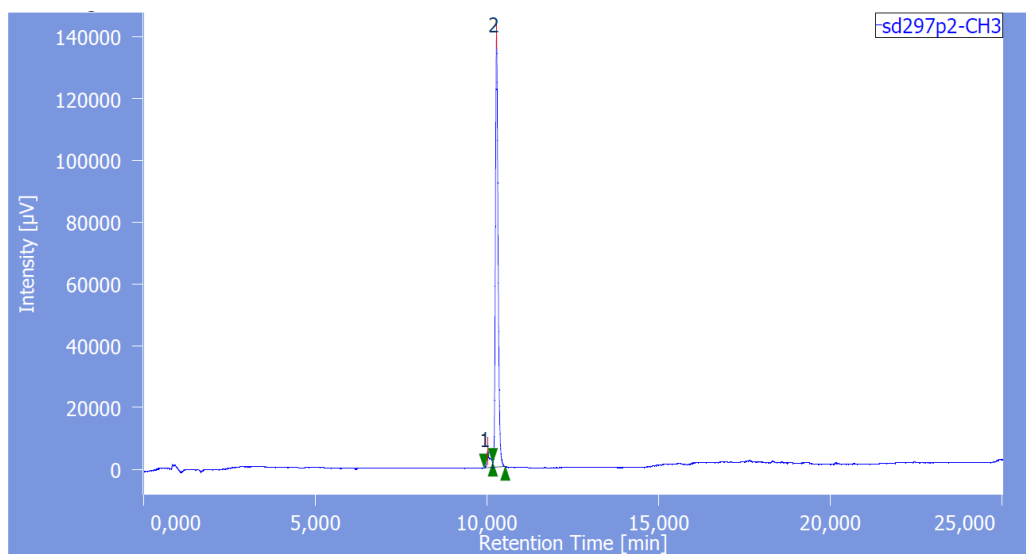
Figure S13: **M-4** after 30 min at room temperature. Product peak accounts for 94.6% of total area (89.1% de).



Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	3	9.850	40667	4684	5.184	3.532	N/A	21362	1.520	N/A	
2	Unknown	3	10.167	743770	127947	94.816	96.468	N/A	75194	N/A	1.251	

Figure S14: **M-4** after 72 h at room temperature. Product peak accounts for 94.8% of total area (89.6% de).



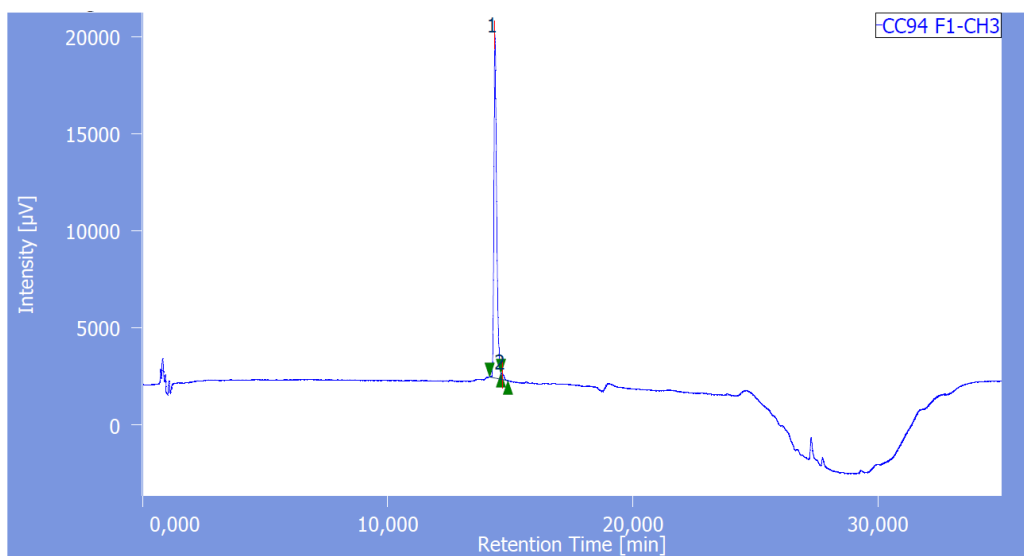
Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	3	10,017	40225	5309	5.130	3.656	N/A	26150	1,352	N/A	
2	Unknown	3	10,275	743912	139892	94.870	96.344	N/A	92123	N/A	1.267	

Figure S15: *M-4* after 5 days at room temperature. Product peak accounts for 94.9% of total area (89.7% de).

Compound 5

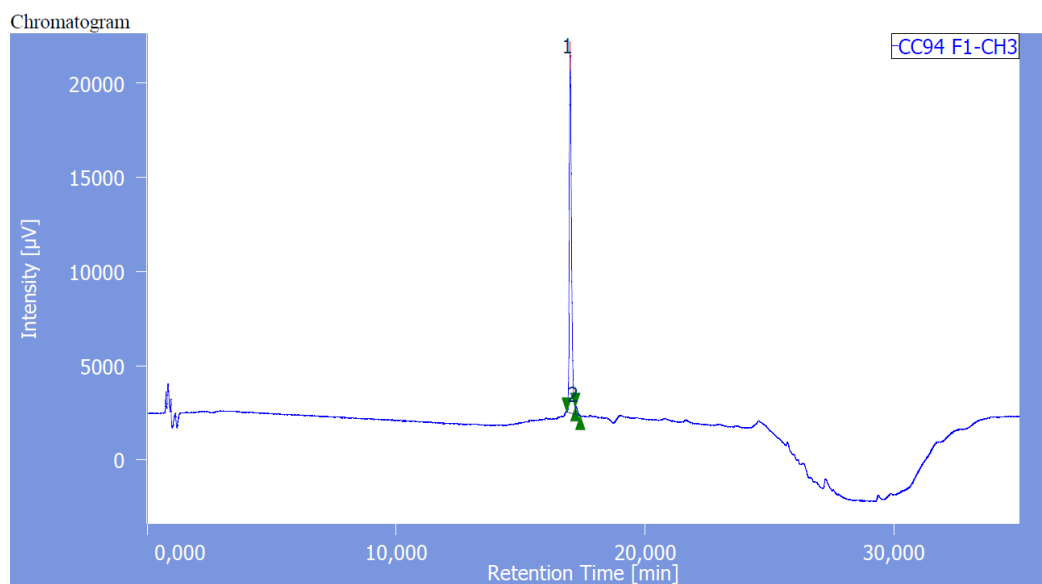
P-5 and *M-5* were dissolved in DMSO to approximately 10 mM concentration, then immediately diluted with H₂O to 60 µM concentration and analyzed by RP-HPLC using System C after 30 minutes, 72 hours and 5 days at room temperature (Figures S16 – S21, showing response at 300 nm).



Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	3	14.367	140788	17675	98.415	98.415	N/A	79670	N/A	1.451	
2	Unknown	3	14.683	2268	285	1.585	1.585	N/A	N/A	N/A	N/A	

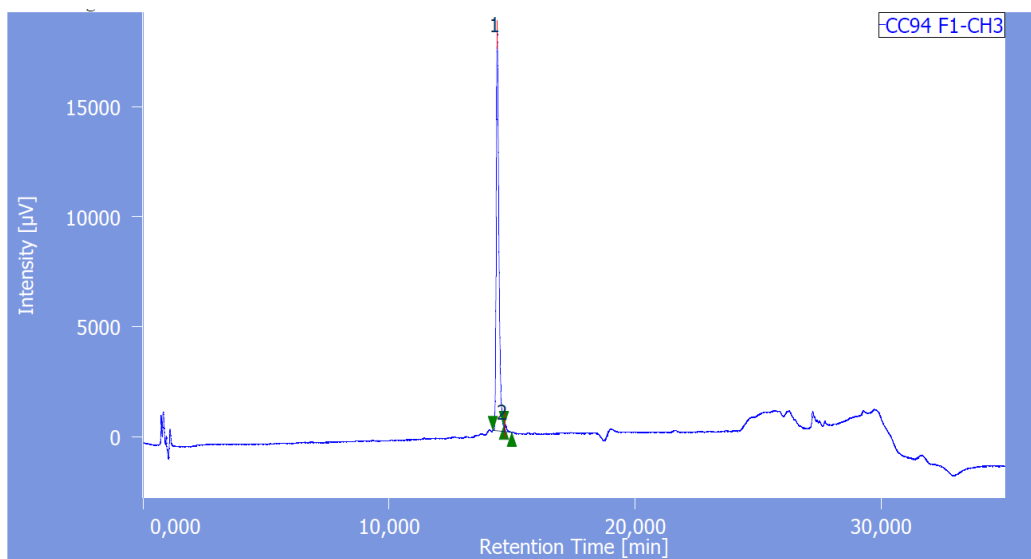
Figure S16: *P-5* after 30 min at room temperature. Product peak accounts for 98.4% of total area (96.8% de).



Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	3	16.983	115187	18934	98.043	97.786	N/A	190357	N/A	1.455	
2	Unknown	3	17.217	2299	429	1.957	2.214	N/A	N/A	N/A	N/A	

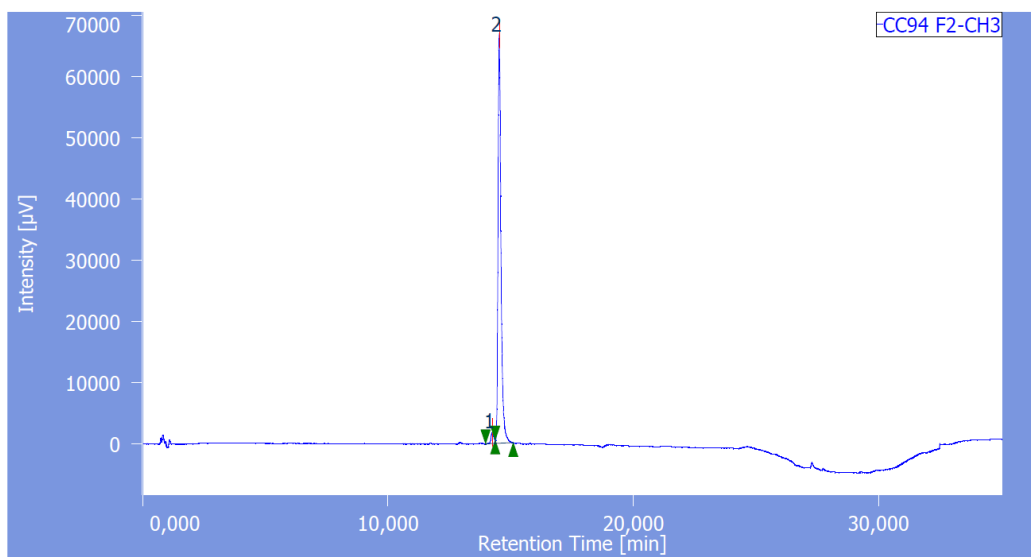
Figure S17: *P-5* after 72 h at room temperature. Product peak accounts for 98.0% of total area (96.1% de).



Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	3	14.392	137809	17993	98.232	98.120	N/A	87790	N/A	1.386	
2	Unknown	3	14.700	2481	345	1.768	1.880	N/A	N/A	N/A	N/A	

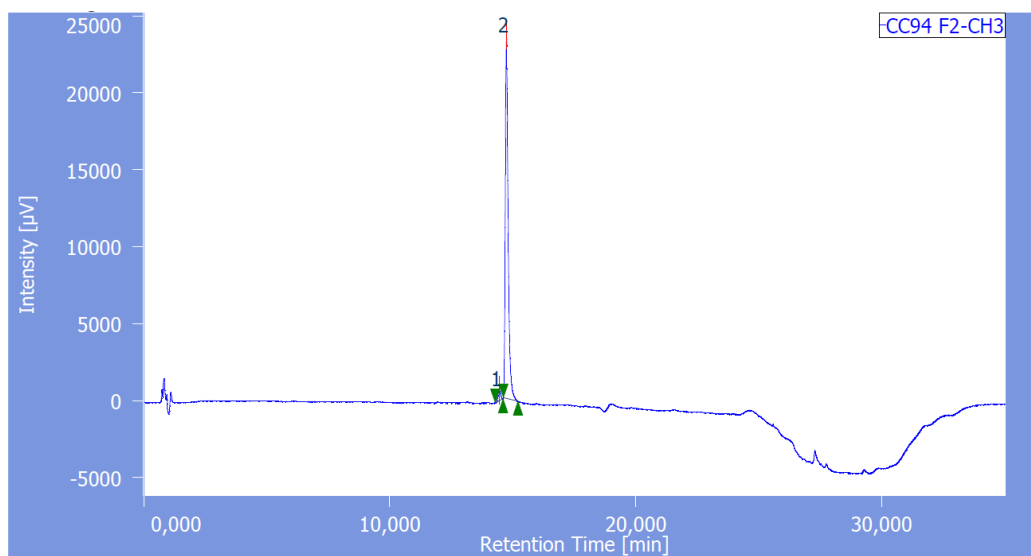
Figure S18: *P-5* after 5 days at room temperature. Product peak accounts for 98.2% of total area (96.5% de).



Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	3	14.242	15123	1816	2.600	2.643	N/A	64361	1.309	N/A	
2	Unknown	3	14.525	566451	66919	97.400	97.357	N/A	76929	N/A	1.521	

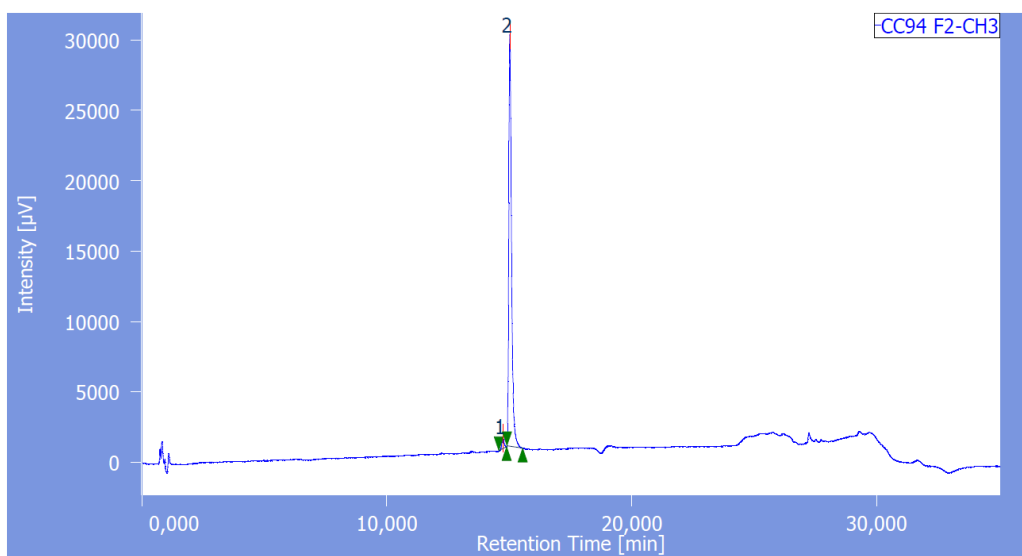
Figure S19: *M-5* after 30 min at room temperature. Product peak accounts for 97.4% of total area (94.8% de).



Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	3	14.442	4878	695	2.480	2.857	N/A	88361	1.476	1.182	
2	Unknown	3	14.733	191789	23618	97.520	97.143	N/A	85134	N/A	1.532	

Figure S20: *M-5* after 72 h at room temperature. Product peak accounts for 97.5% of total area (95.0% de).



Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	3	14.733	4909	730	2.124	2.435	N/A	109456	1.535	1.105	
2	Unknown	3	15.017	226176	29240	97.876	97.565	N/A	97916	N/A	1.524	

Figure S21: *M-5* after 5 days at room temperature. Product peak accounts for 97.9% of total area (95.4% de).

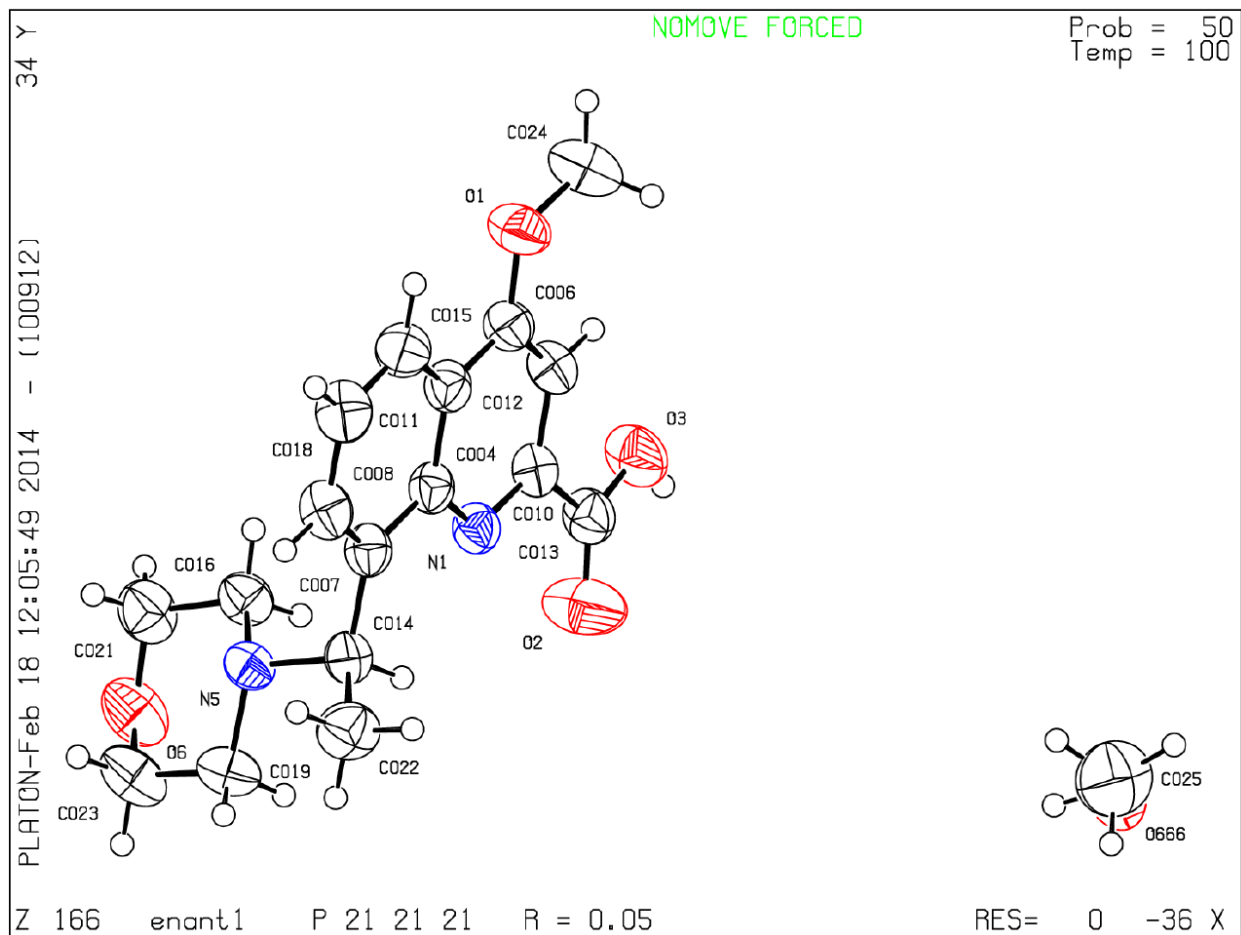
S4 Crystallography

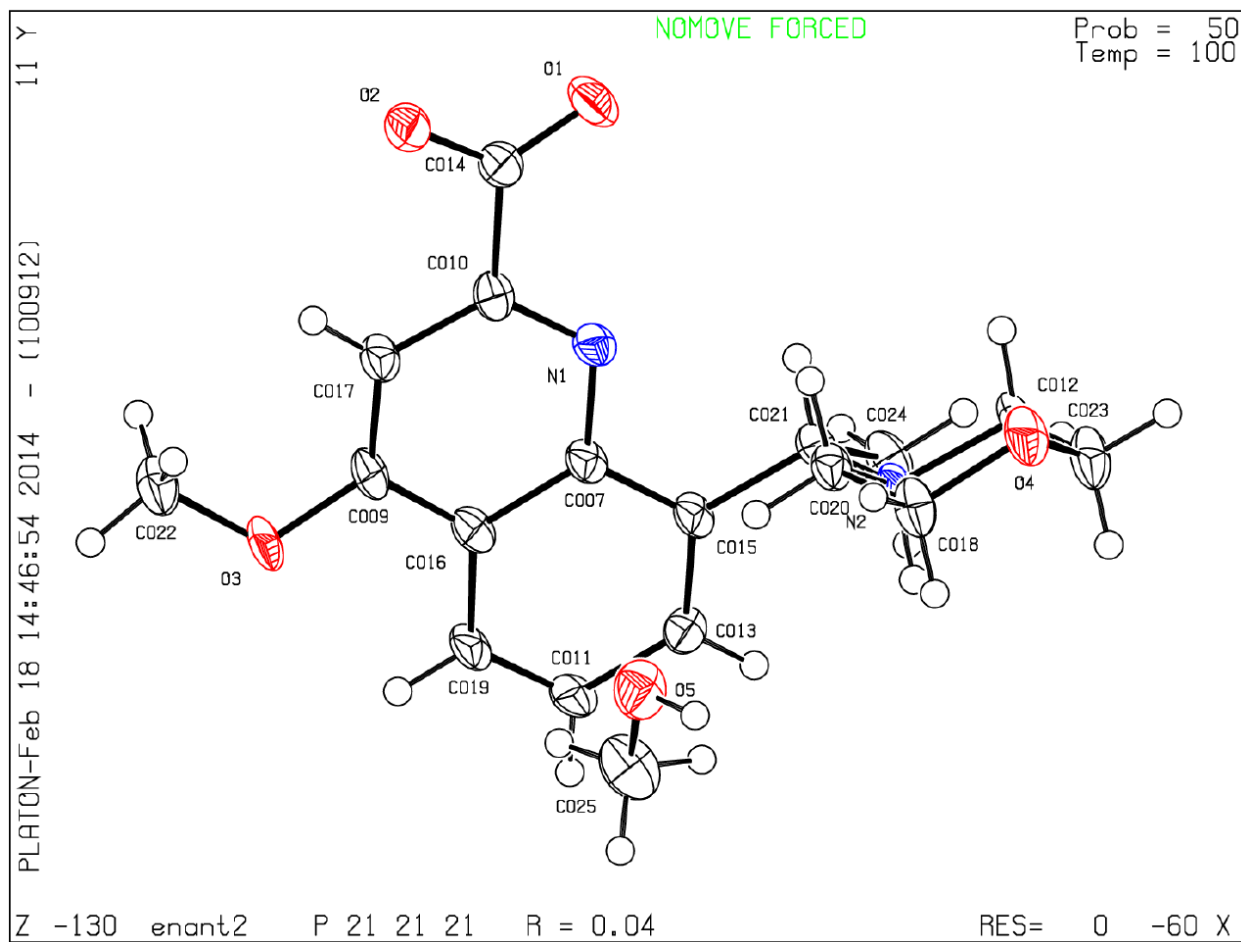
R-Q_{Morph} and **S-Q_{Morph}** monomers were crystallized via liquid-liquid diffusion of Et₂O into a solution of the compound in CH₂Cl₂. X-ray analyses were carried out at the IECB X-ray facility (UMS 3033 CNRS, INSERM US001, Bordeaux University) on a High flux RIGAKU FRX rotating anode at the Cu K α wavelength. The diffractometer was equipped with a partial Chi 3 circles goniometer and a hybrid pixel detector DECTRIS PILATUS[®] 200K 20Hz. The crystals of both enantiomers were collected at 100 K and mounted on cryo-loops after quick soaking on Paratone-N oil from Hampton research before flash-frozen. The data were processed using the RIGAKU CrystalClear[®] suite version 2.1 b25.^[2] Both structures were solved using the charge flipping algorithm implemented in SUPERFLIP^[3] and refined using SHELX-2013 through the integrated WinGX system.^[4] The positions of most of the H atoms were determined from fourier difference maps analysis or deduced from coordinates of the non-H atoms and confirmed by Fourier synthesis. H atoms were included for structure factor calculations and their positions refined for some of them (see cif files). The non-H atoms were refined with anisotropic temperature parameters. The **S-Q_{Morph}** monomer crystallized as a zwitterion.

Data statistics are shown in Table S1.

Name	<i>R</i> - <i>Q</i> _{Morph}	<i>S</i> - <i>Q</i> _{Morph}
CCDC number	990870	990871
Formula	C ₁₈ H ₂₄ N ₂ O ₅	C ₁₈ H ₂₄ N ₂ O ₅
M	348.39	348.39
Crystal system	P2 ₁ 2 ₁ 2 ₁	P2 ₁ 2 ₁ 2 ₁
Space group	orthorhombic	orthorhombic
<i>a</i> /Å	8.7300(17)	8.7041(17)
<i>b</i> /Å	11.006(2)	10.823(2)
<i>c</i> /Å	18.862(4)	18.873(4)
U/Å ³	1812.3(6)	1778(6)
T /K	100(2)	100(2)
Z	4	4
ρ/g cm ⁻¹	1.277	1.301
Size (mm)	0.1 x 0.05 x 0.05	0.05 x 0.03 x 0.001
λ / Å	1.5419	1.5419
μ/mm ⁻¹	0.772	0.787
Unique data	3275	2400
Parameters / Restraints	234 / 0	230 / 0
Final R indices [I>2σ(I)]	R1 = 0.0472, wR2 = 0.1336	R1 = 0.0418, wR2 = 0.1016
Flack factor	0.02(10)	0.12(6)
Goodness of fit	1.077	1.002

Table S1: X-ray crystallographic data.

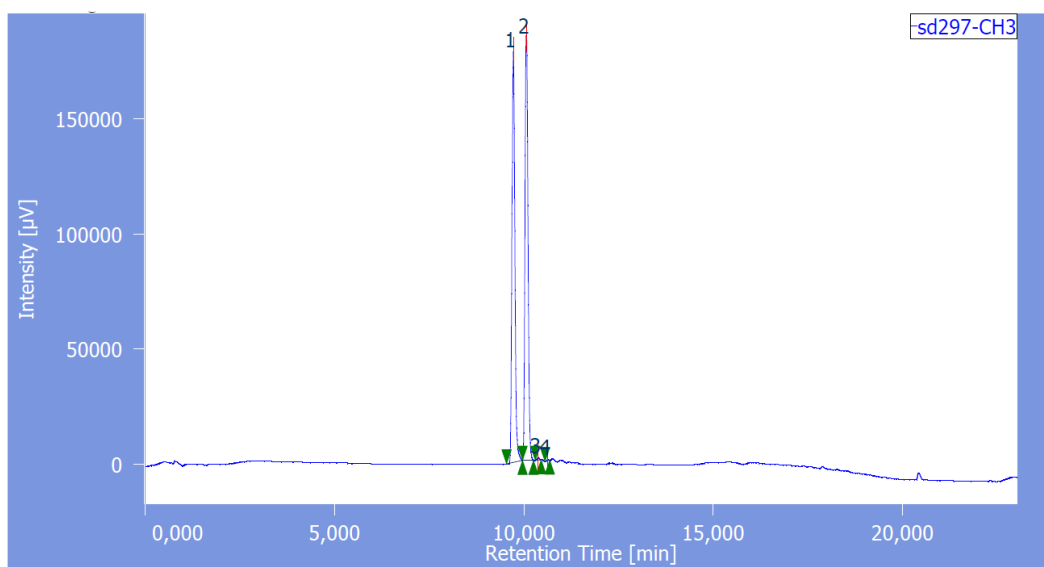




S5 Chromatographic data

RP-HPLC analyses were performed at 1.5 mL min⁻¹ using a Machery-Nagel Nucleodur C18 or C8 Gravity column (4.6 x 100 mm, 3 μm). The mobile phase was composed of 0.1% (v/v) TFA-H₂O (Solvent A) and 0.1% TFA-CH₃CN (Solvent B) running the following gradients: 5–30% B over 13 min, then 30–100% B over 5 min (System A), 5–100% B over 13 min then 100% B for 5 min (System B), or 20–60% B over 25 min then 60–100% B for 5 min (System C). Monitoring by UV detection was carried out at 214 nm, 254 nm and 300 nm using a diode array detector.

Compound 4 (crude)

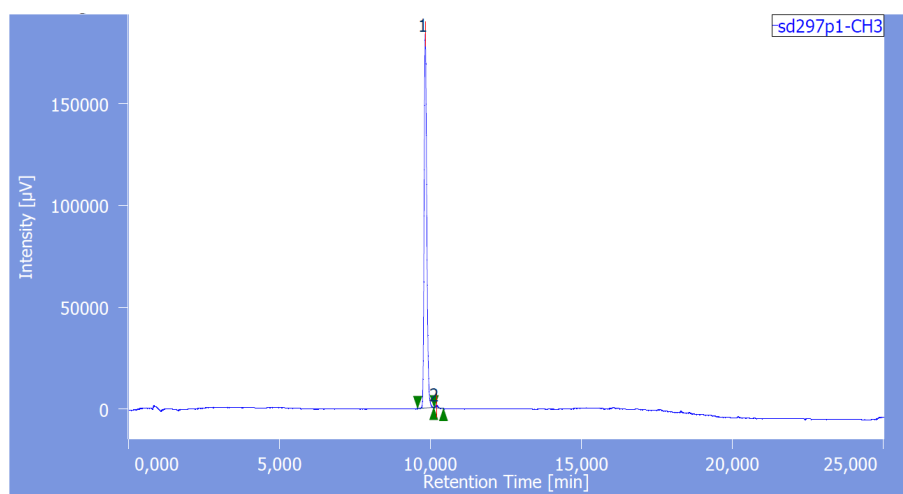


Peak Information

#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor
1	Unknown	3	9.717	957540	178118	48.744	49.025	N/A	75635	2.453	1.196
2	Unknown	3	10.067	999820	183418	50.897	50.484	N/A	77322	2.404	1.119
3	Unknown	3	10.375	5104	1250	0.260	0.344	N/A	136335	2.402	0.954
4	Unknown	3	10.633	1947	535	0.099	0.147	N/A	169676	N/A	0.900

Figure S22: Chromatogram of crude 4 (System A, 300 nm).

Compound *P-4*

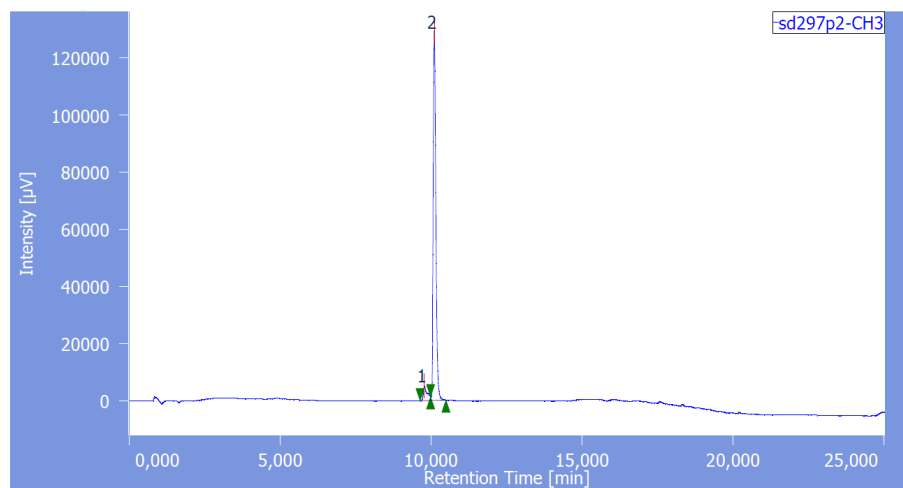


Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	3	9.825	1102111	183803	99.332	99.227	N/A	61529	2.500	1.260	
2	Unknown	3	10.200	7412	1433	0.668	0.773	N/A	82091	N/A	1.238	

Figure S23: Chromatogram of *P-4* (System A, 300 nm). Purity = 99%.

Compound *M-4*

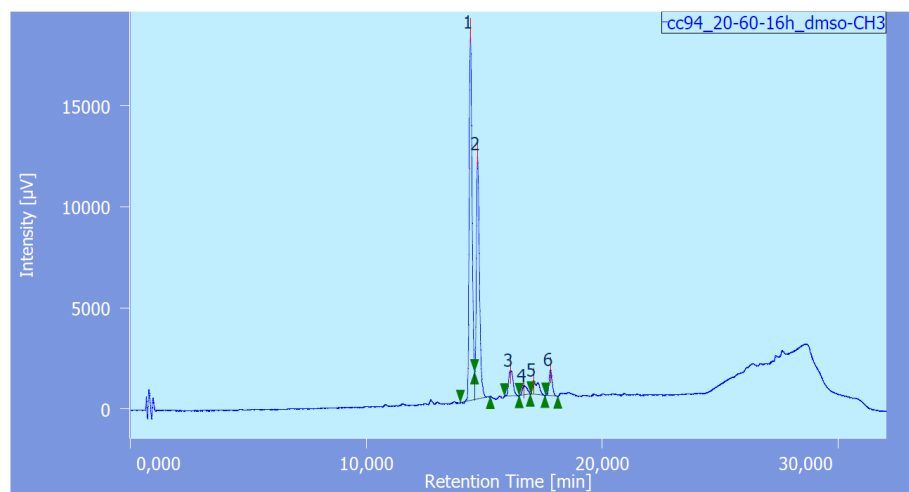


Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	3	9.775	45476	5113	5.430	3.804	N/A	21298	1.567	N/A	
2	Unknown	3	10.108	792021	129290	94.570	96.196	N/A	65040	N/A	1.245	

Figure S24: Chromatogram of *M-4* (System A, 300 nm). Purity = 95%.

Compound 5 (crude)

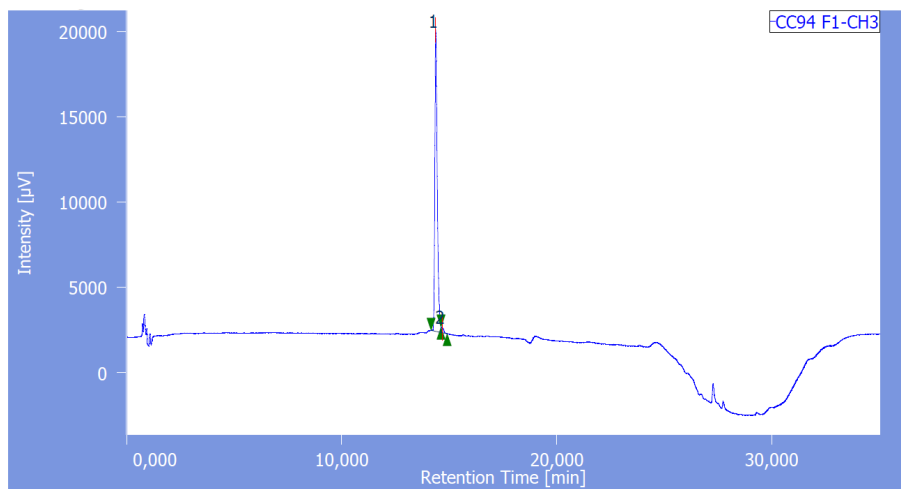


Peak Information

#	Peak Name	CH	tR [min]	Area [$\mu\text{V}\cdot\text{sec}$]	Height [μV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	3	14.400	156556	18293	49.877	53.742	N/A	64999	1.357	N/A	
2	Unknown	3	14.708	110149	12107	35.093	35.567	N/A	65530	4.769	N/A	
3	Unknown	3	16.108	16454	1234	5.242	3.625	N/A	32234	1.478	1.264	
4	Unknown	3	16.675	6664	460	2.123	1.352	N/A	26498	0.845	1.242	
5	Unknown	3	17.083	12164	676	3.875	1.985	N/A	14929	1.779	2.359	
6	Unknown	3	17.792	11893	1269	3.789	3.728	N/A	88499	N/A	1.100	

Figure S25: Chromatogram of crude **5** (System C, 300 nm).

Compound P-5

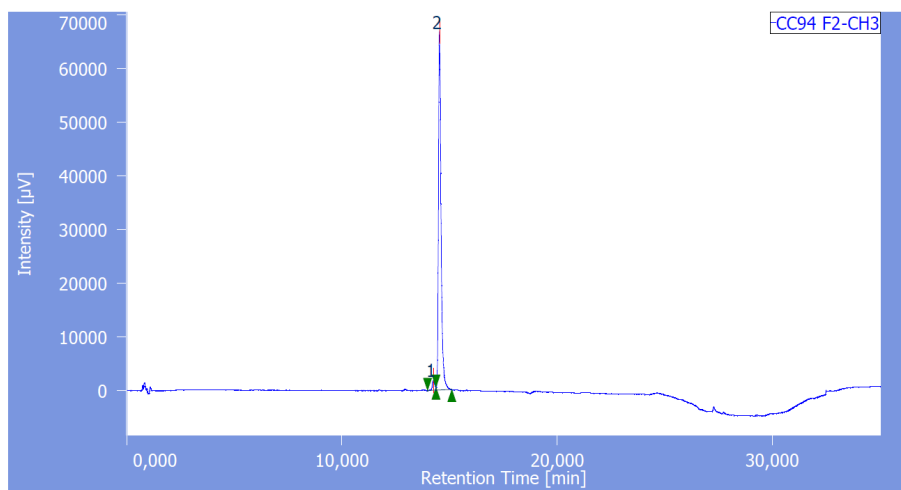


Peak Information

#	Peak Name	CH	tR [min]	Area [$\mu\text{V}\cdot\text{sec}$]	Height [μV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	3	14.367	140788	17675	98.415	98.415	N/A	79670	N/A	1.451	
2	Unknown	3	14.683	2268	285	1.585	1.585	N/A	N/A	N/A	N/A	

Figure S26: Chromatogram of **P-5** (System C, 300 nm). Purity = 98%.

Compound *M-5*

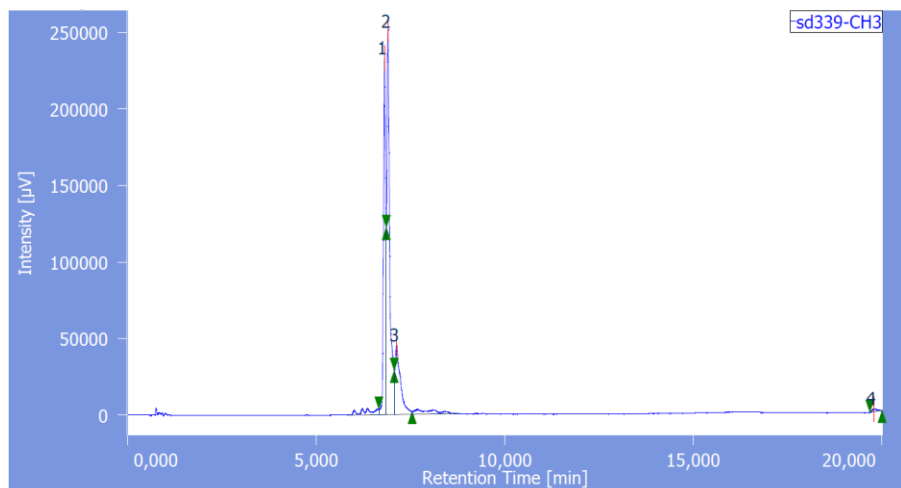


Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	3	14.242	15123	1816	2.600	2.643	N/A	64361	1.309	N/A	
2	Unknown	3	14.523	566451	66919	97.400	97.357	N/A	76929	N/A	1.521	

Figure S27: Chromatogram of *M-5* (System C, 300 nm). Purity = 97%.

Compound 6 (crude)

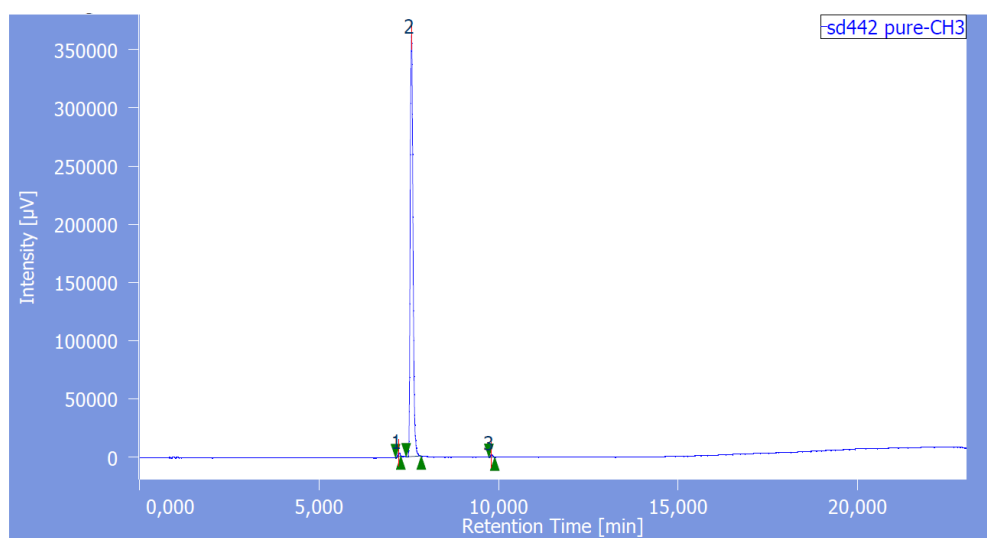


Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	3	6.817	952450	232593	33.967	43.813	N/A	N/A	N/A	N/A	
2	Unknown	3	6.908	1377266	251245	49.118	47.327	N/A	41600	N/A	N/A	
3	Unknown	3	7.133	456300	45286	16.273	8.531	N/A	N/A	N/A	N/A	
4	Unknown	3	19.775	17996	1751	0.642	0.330	N/A	71645	N/A	1.852	

Figure S28: Chromatogram of crude **6** (System B, 300 nm).

Compound 11



Peak Information

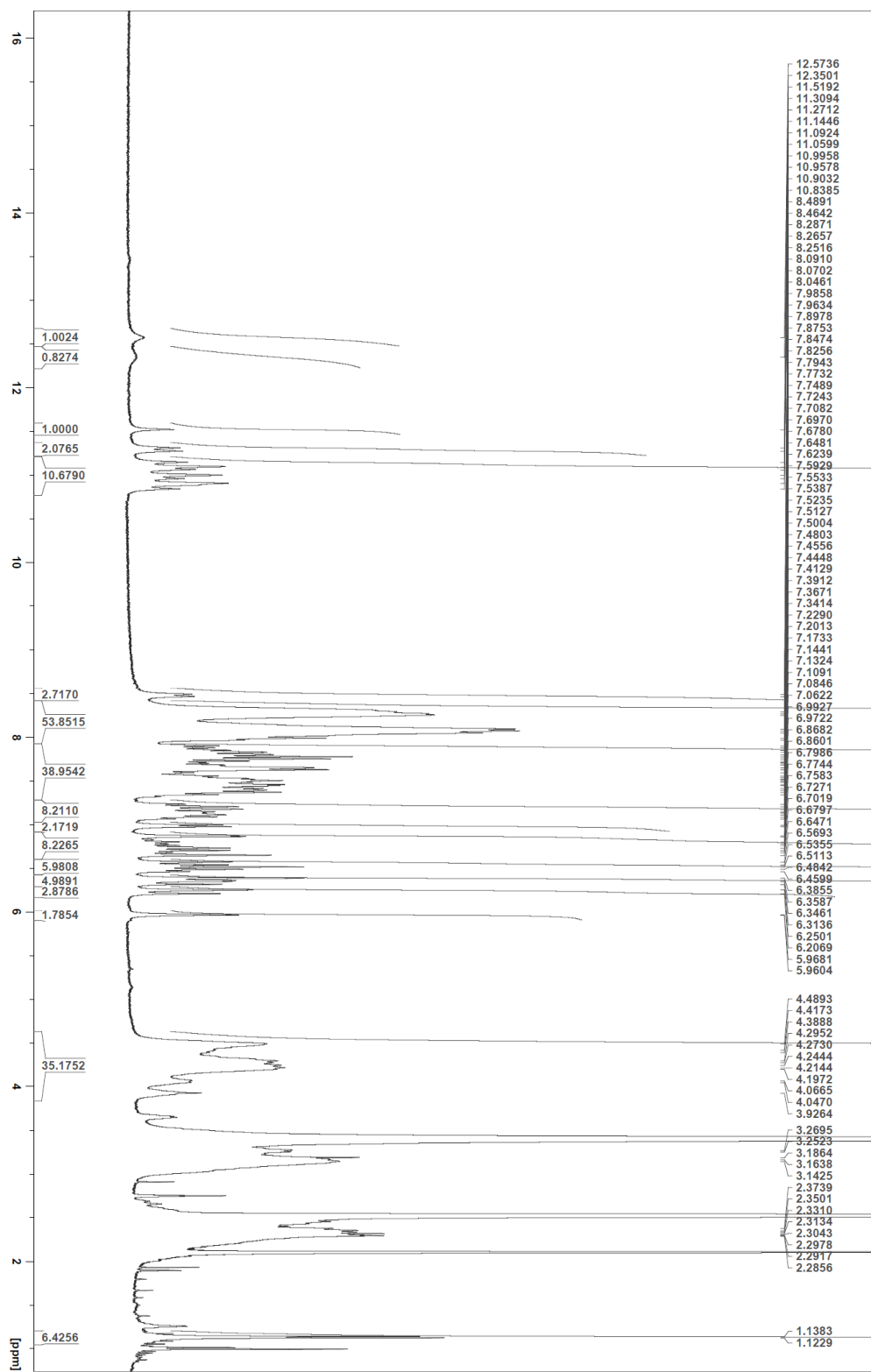
#	Peak Name	CH	tR [min]	Area [µV-sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	3	7.225	13559	3405	0.701	0.928	N/A	65601	2.797	0.982	
2	Unknown	3	7.575	1908834	361204	98.738	98.437	N/A	48110	16.761	1.331	
3	Unknown	3	9.800	10847	2328	0.561	0.635	N/A	93692	N/A	1.113	

Figure S29: Chromatogram of **11** (System A, 300 nm). Purity = 99%.

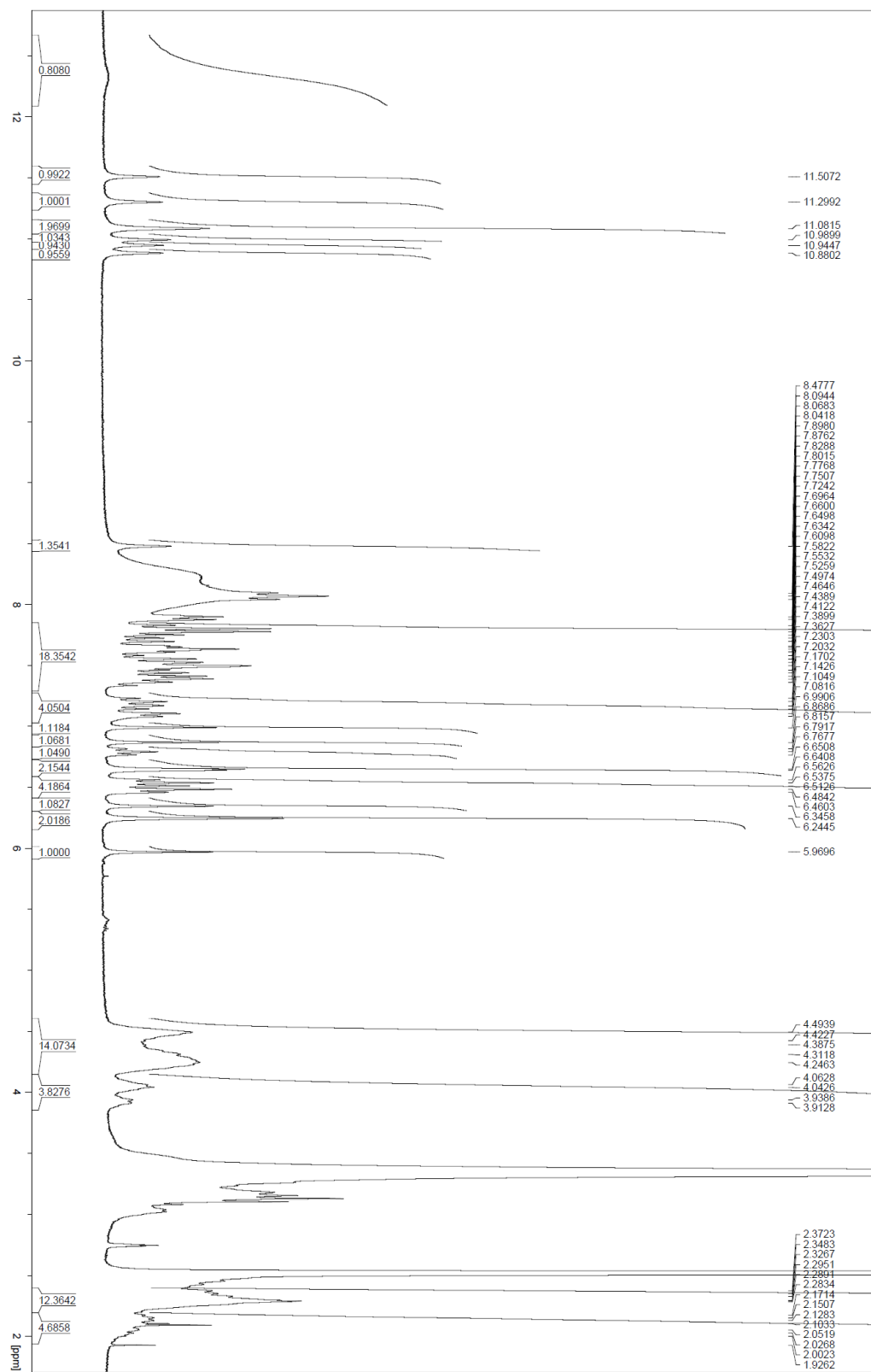
S6 NMR spectra

^1H -NMR spectra were measured at 300, 400 or 500 MHz and ^{13}C -NMR spectra were measured at 75, 100 or 125 MHz. Chemical shifts are reported in ppm and are calibrated against residual solvent signals of CDCl_3 (δ 7.26, 77.2), DMSO-d_6 (δ 2.50, 39.4), or D_2O (δ 4.79). All coupling constants are reported in hertz (Hz). Signals were abbreviated as s, singlet; brs, broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet, dd (doublet of doublets).

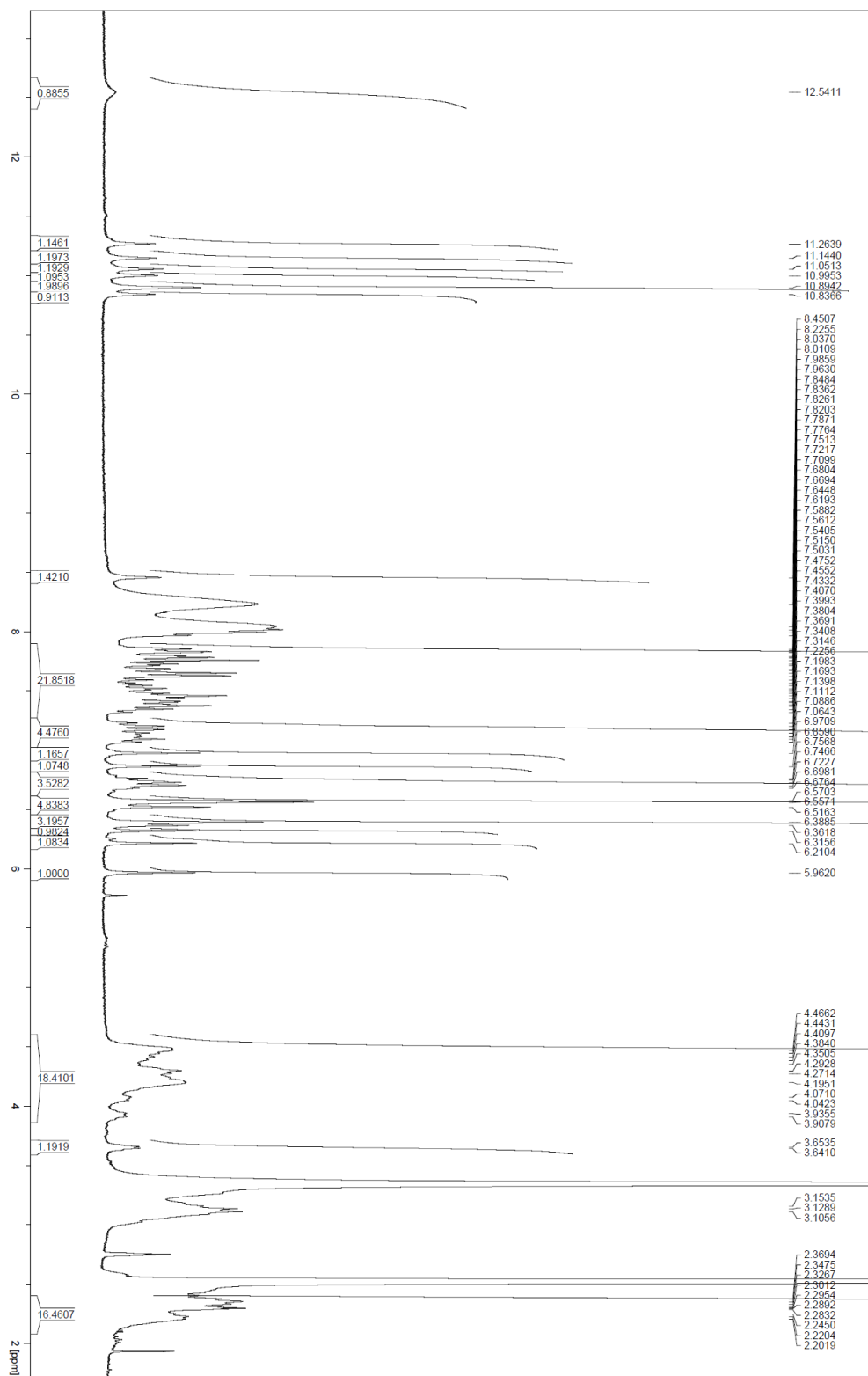
Compound 4 (crude)



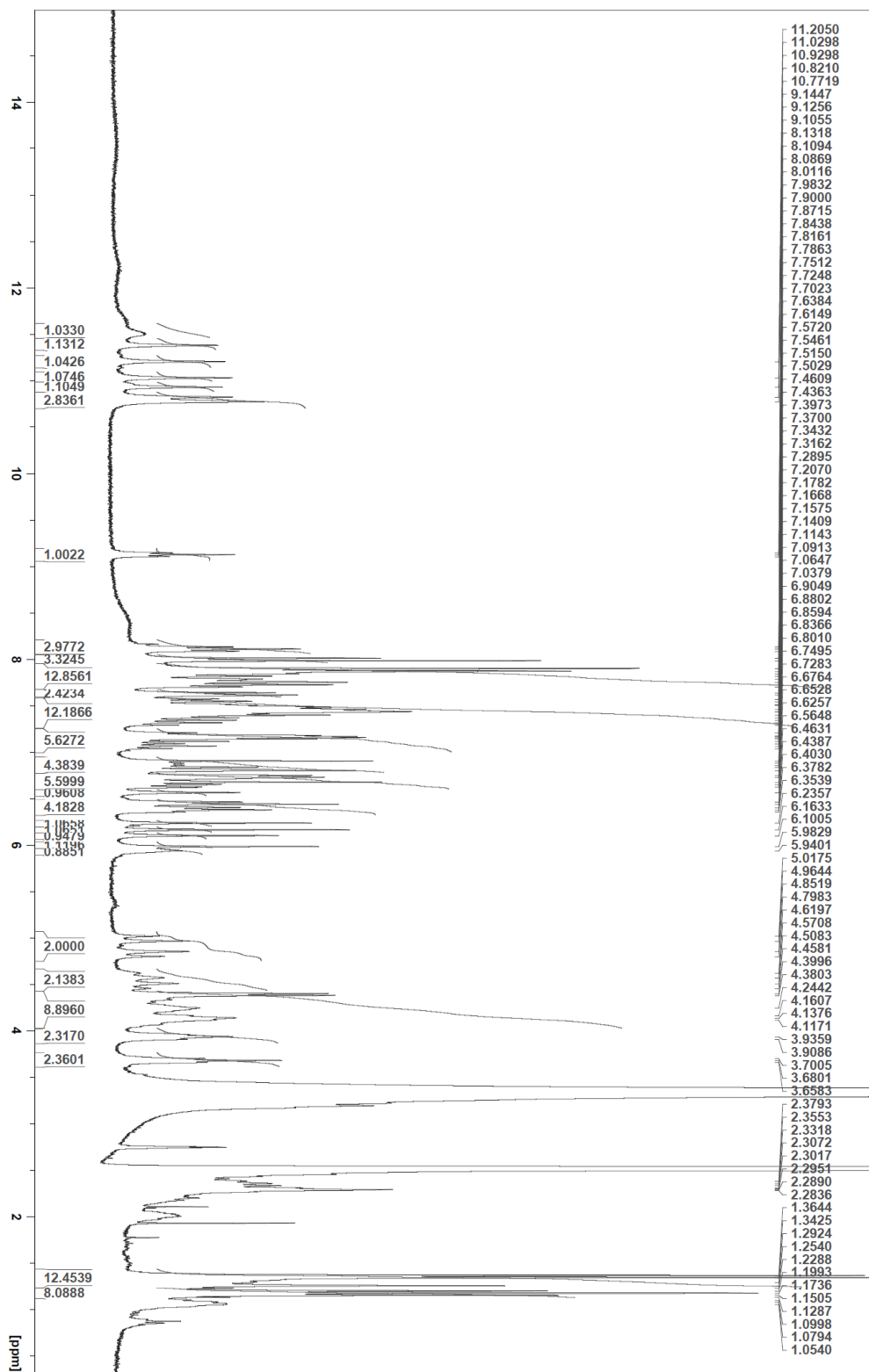
Compound P-4



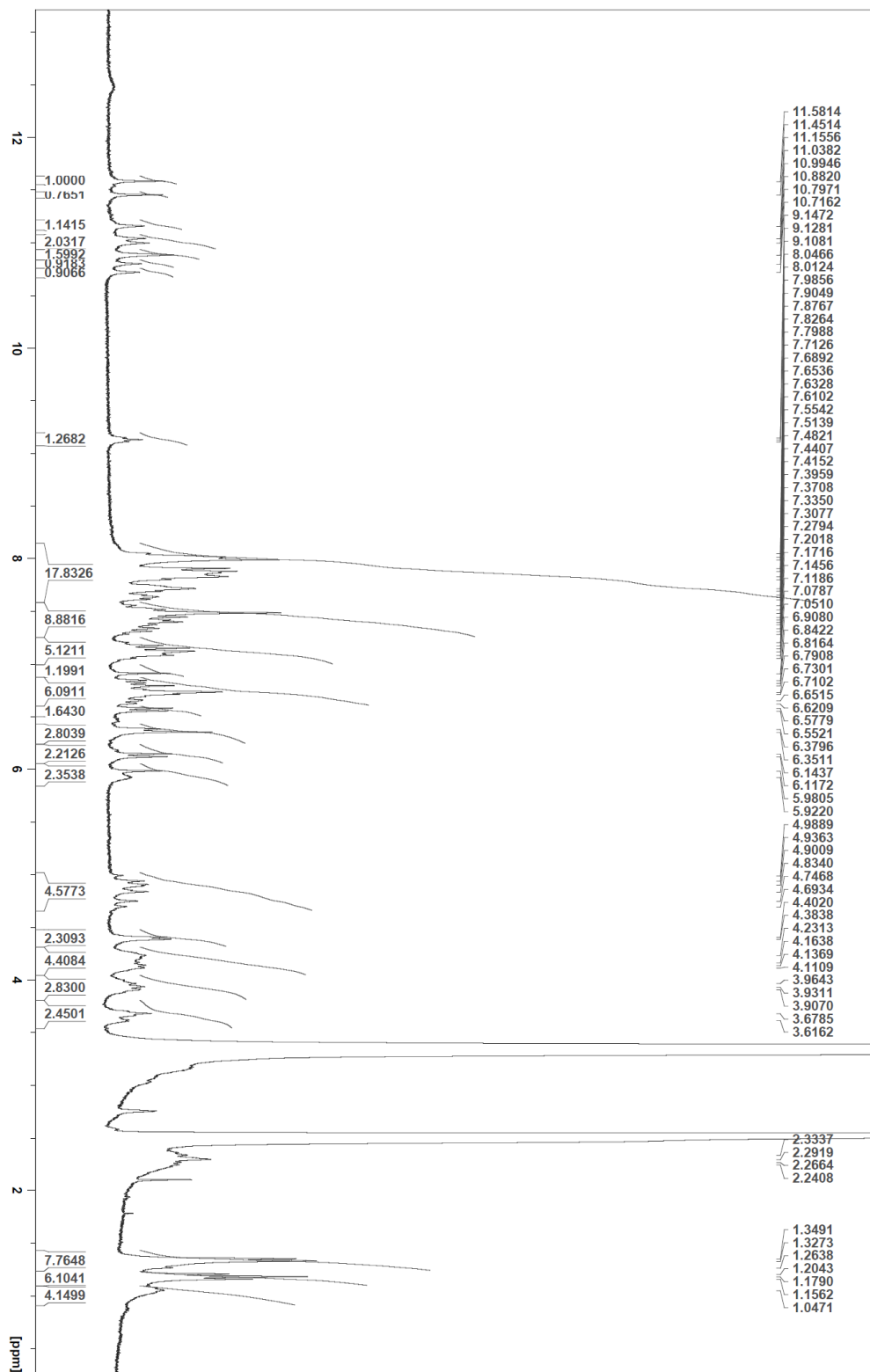
Compound M-4



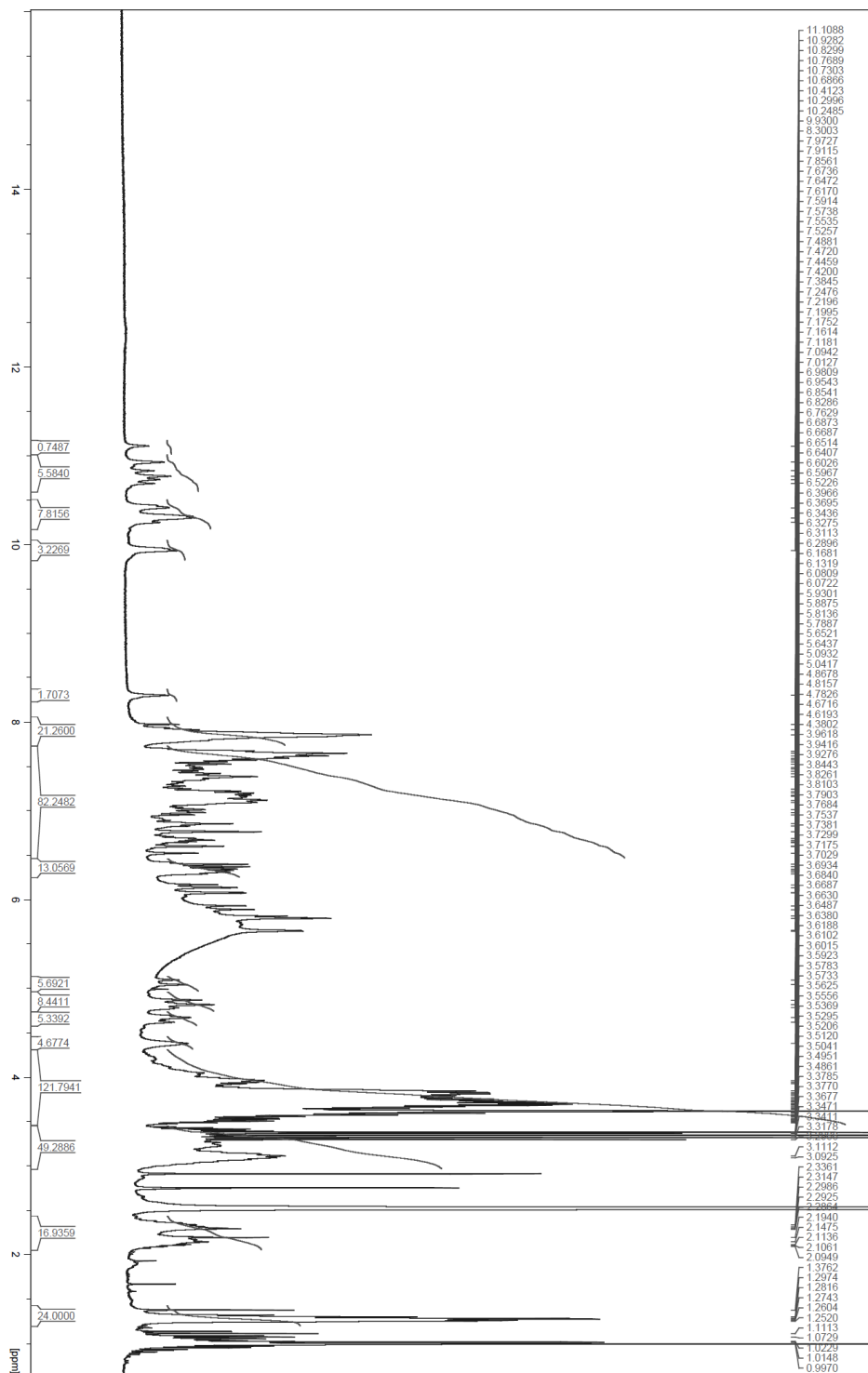
Compound P-5



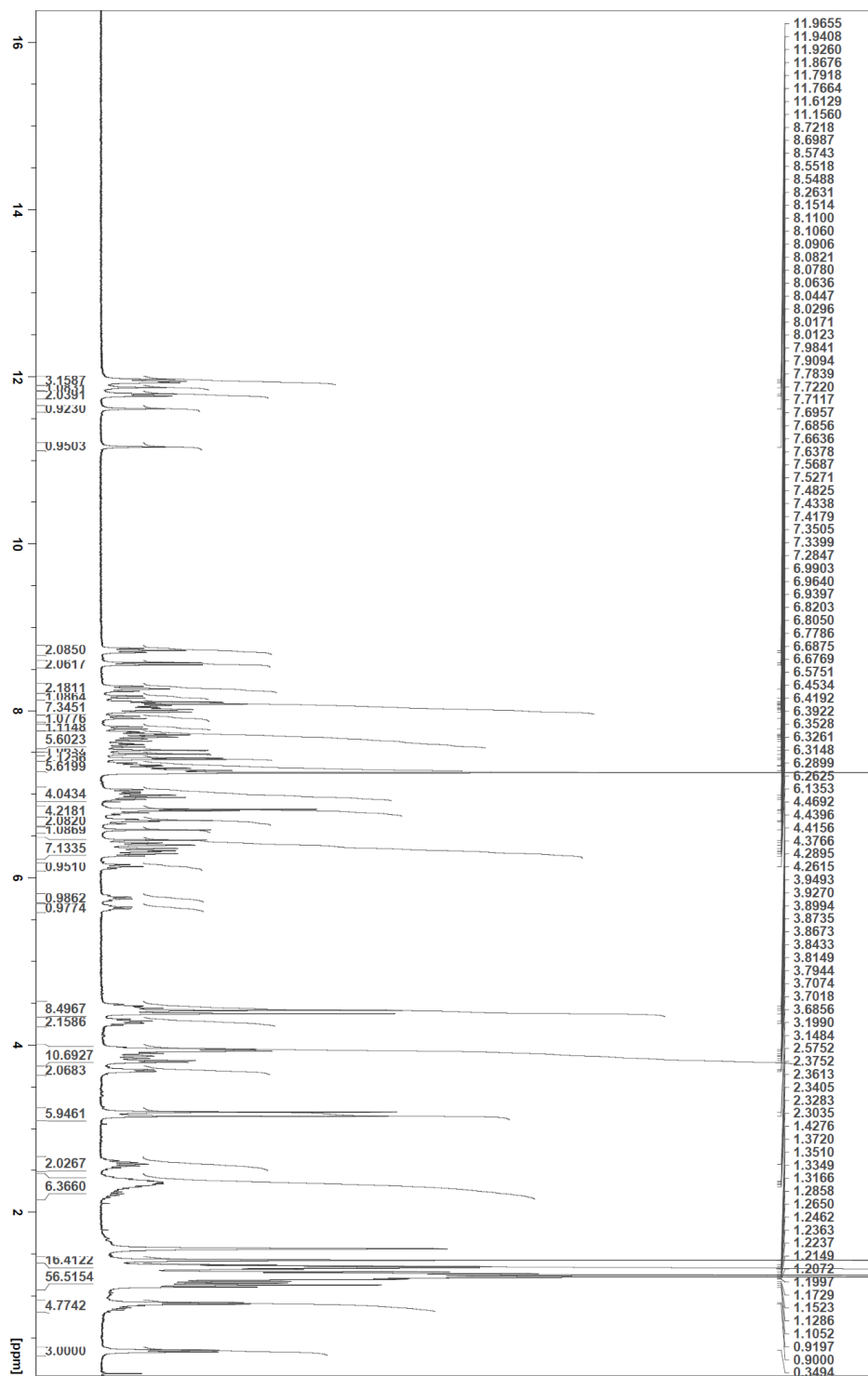
Compound M-5

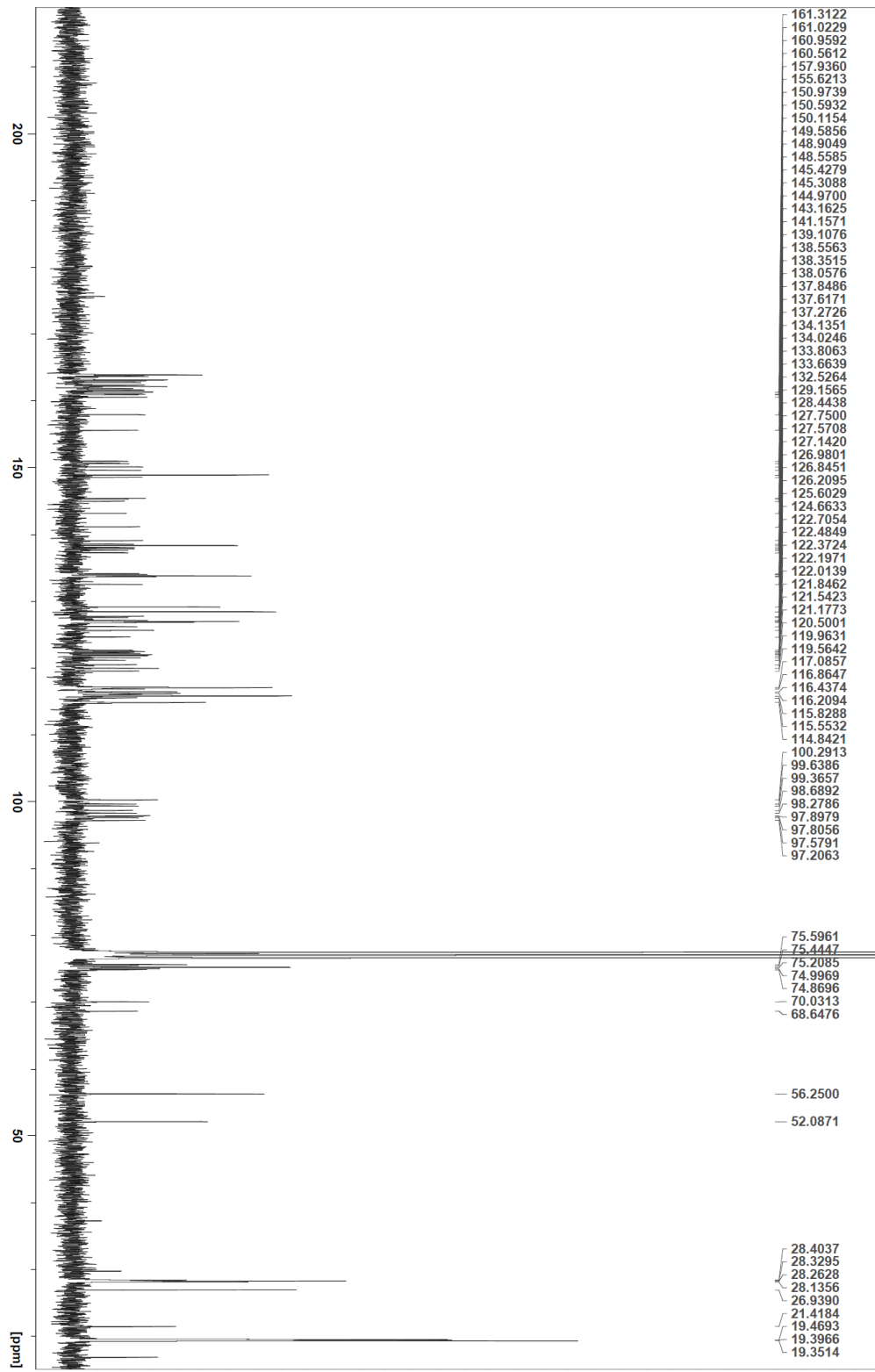


Compound 6

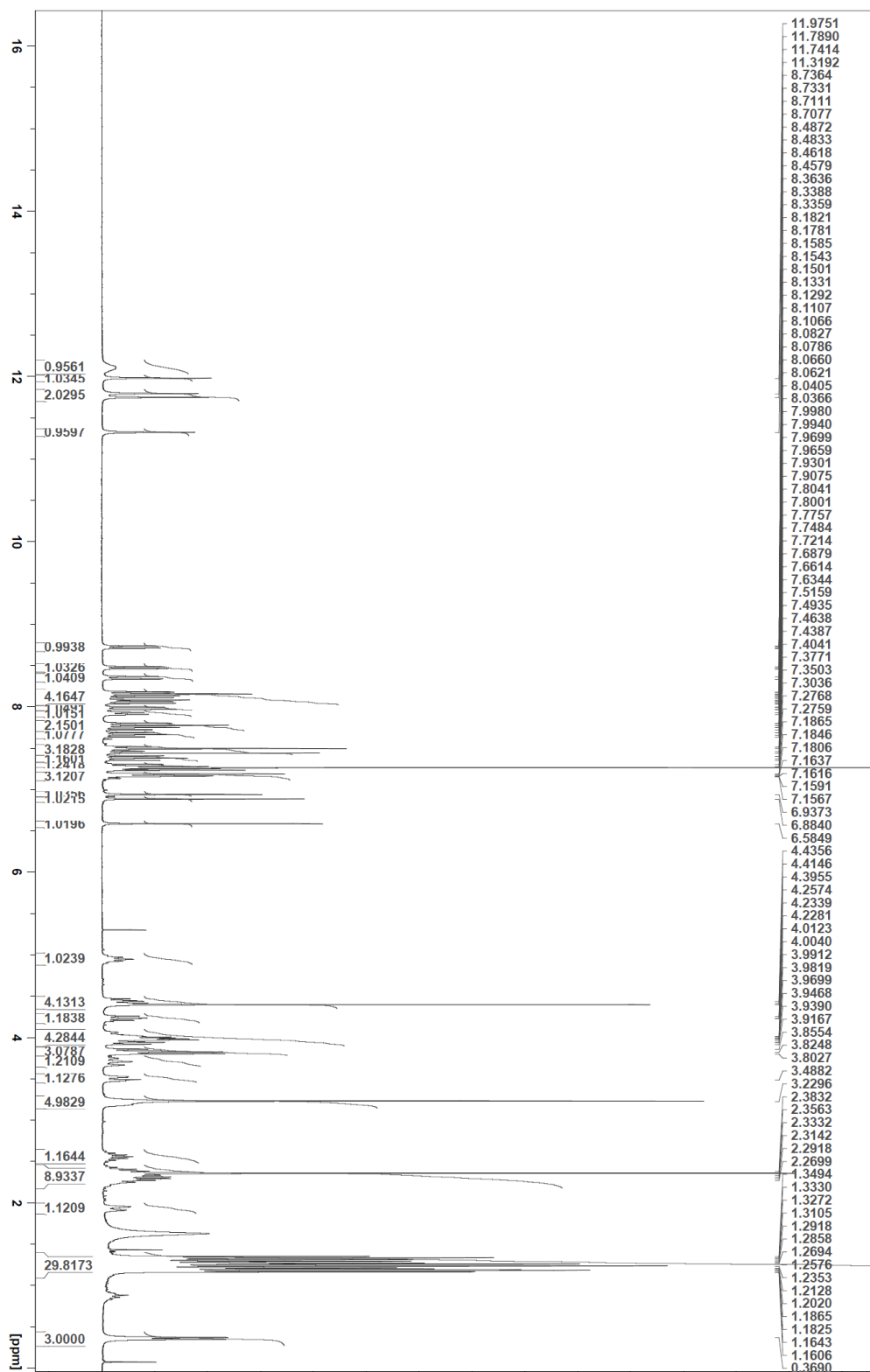


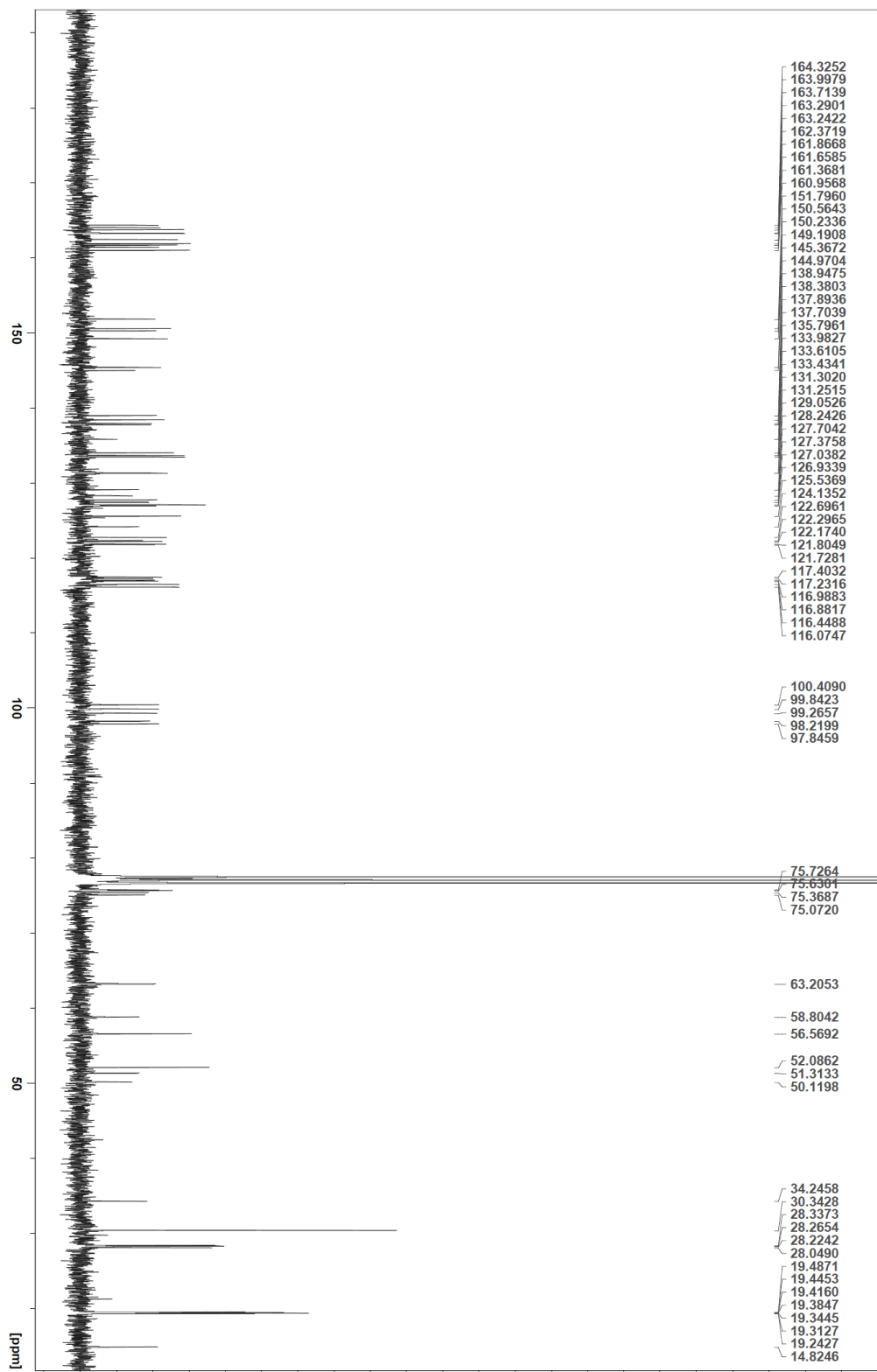
Compound 7



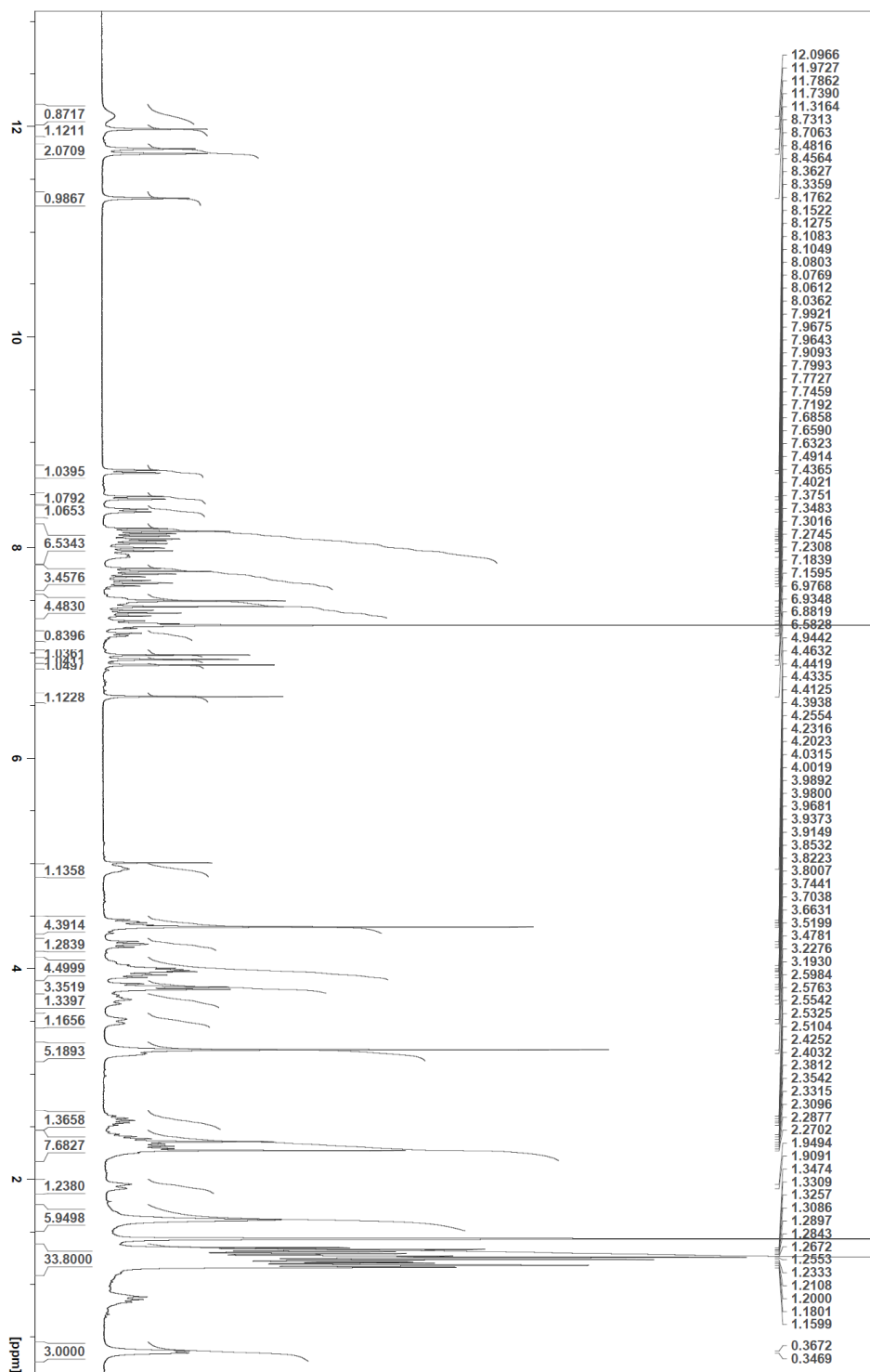


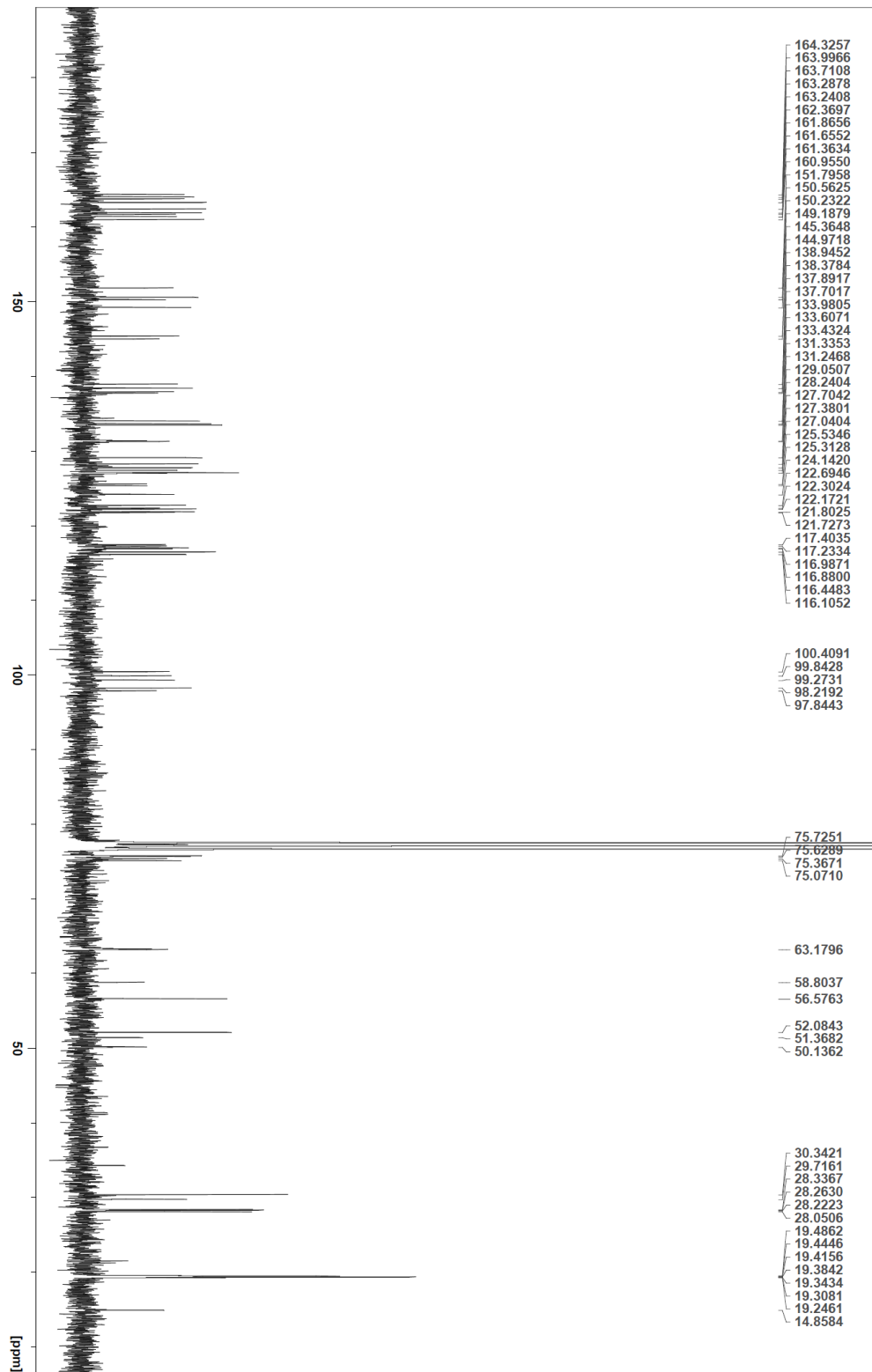
Compound 8



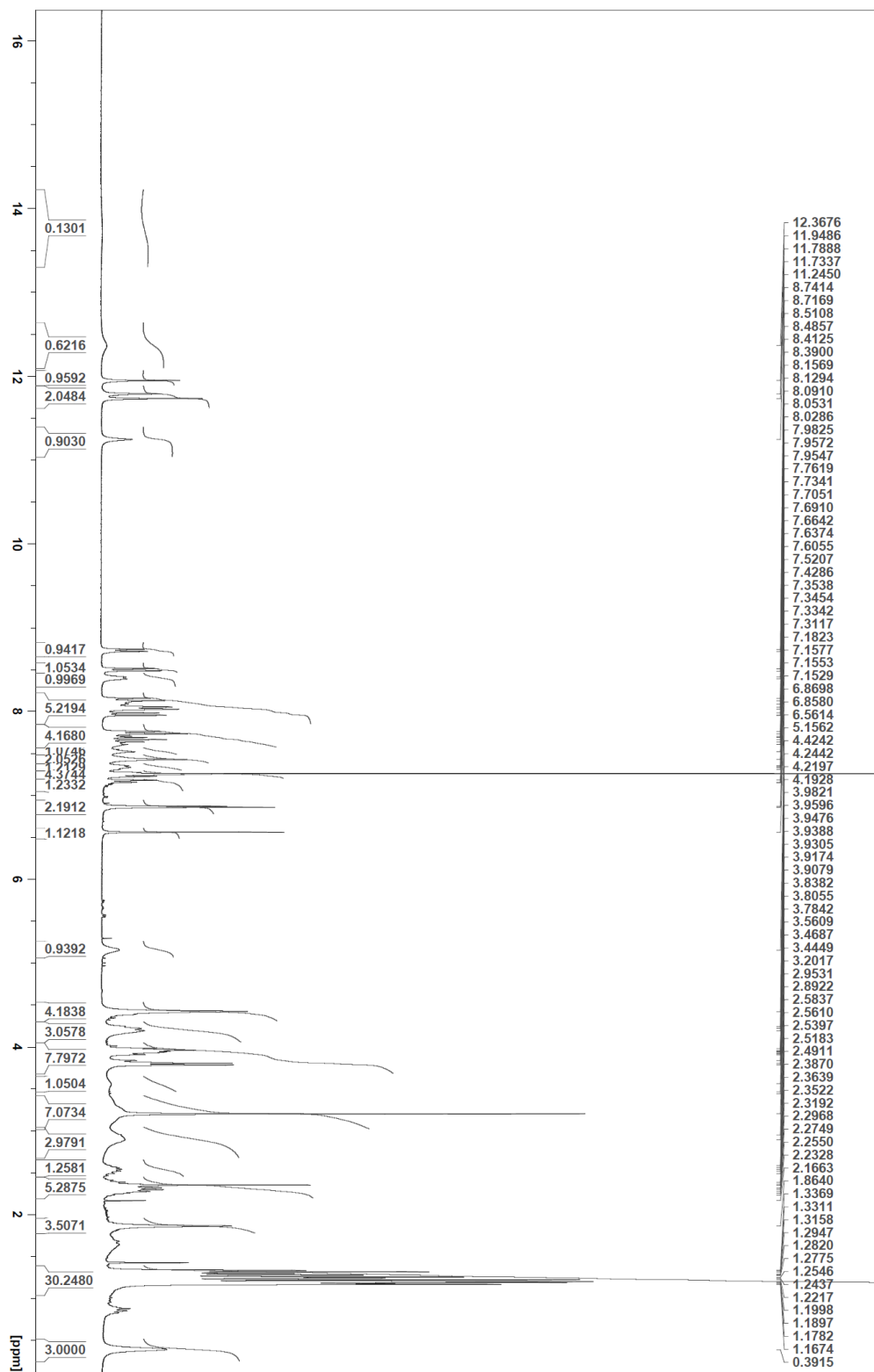


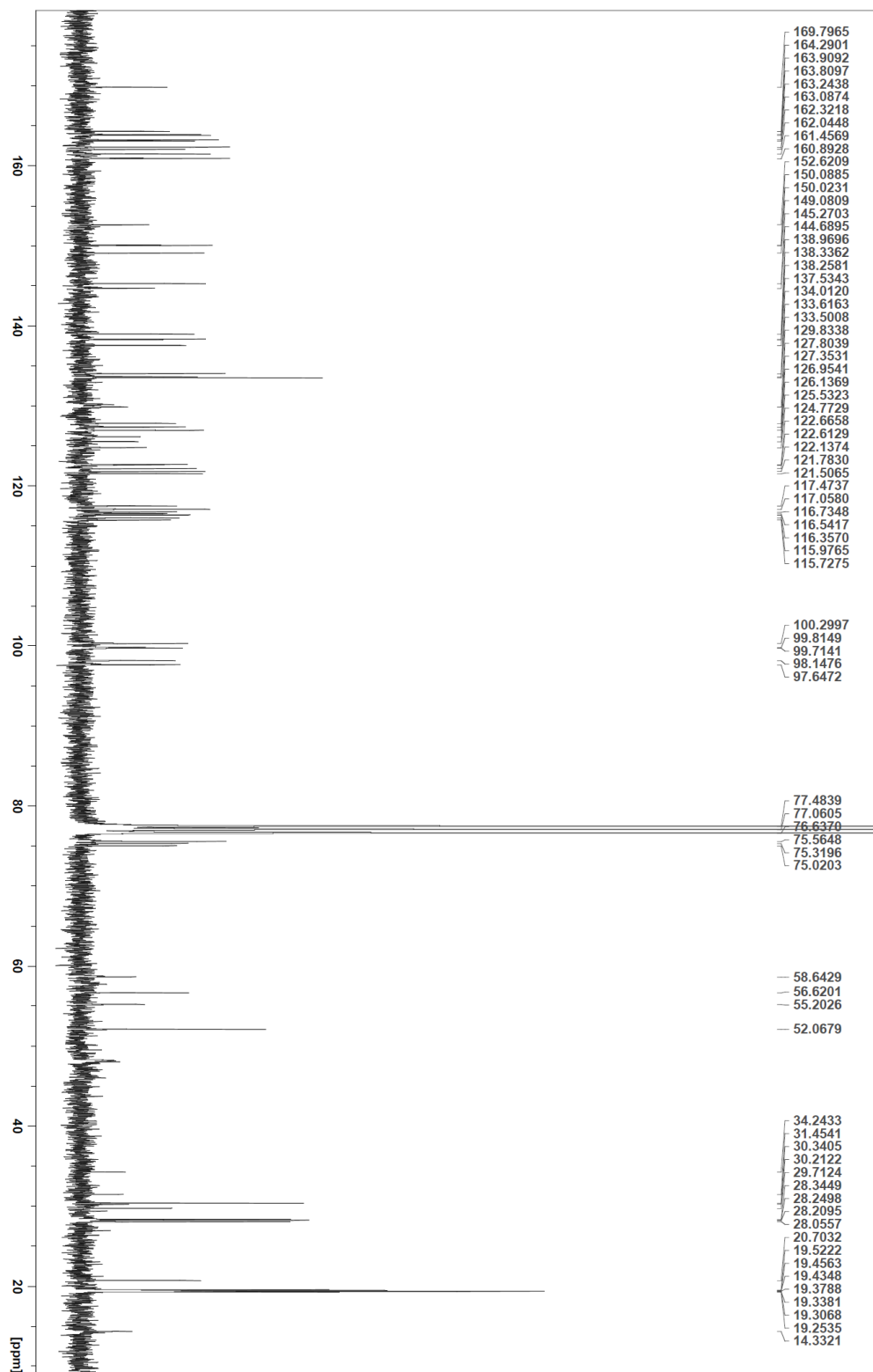
Compound 9



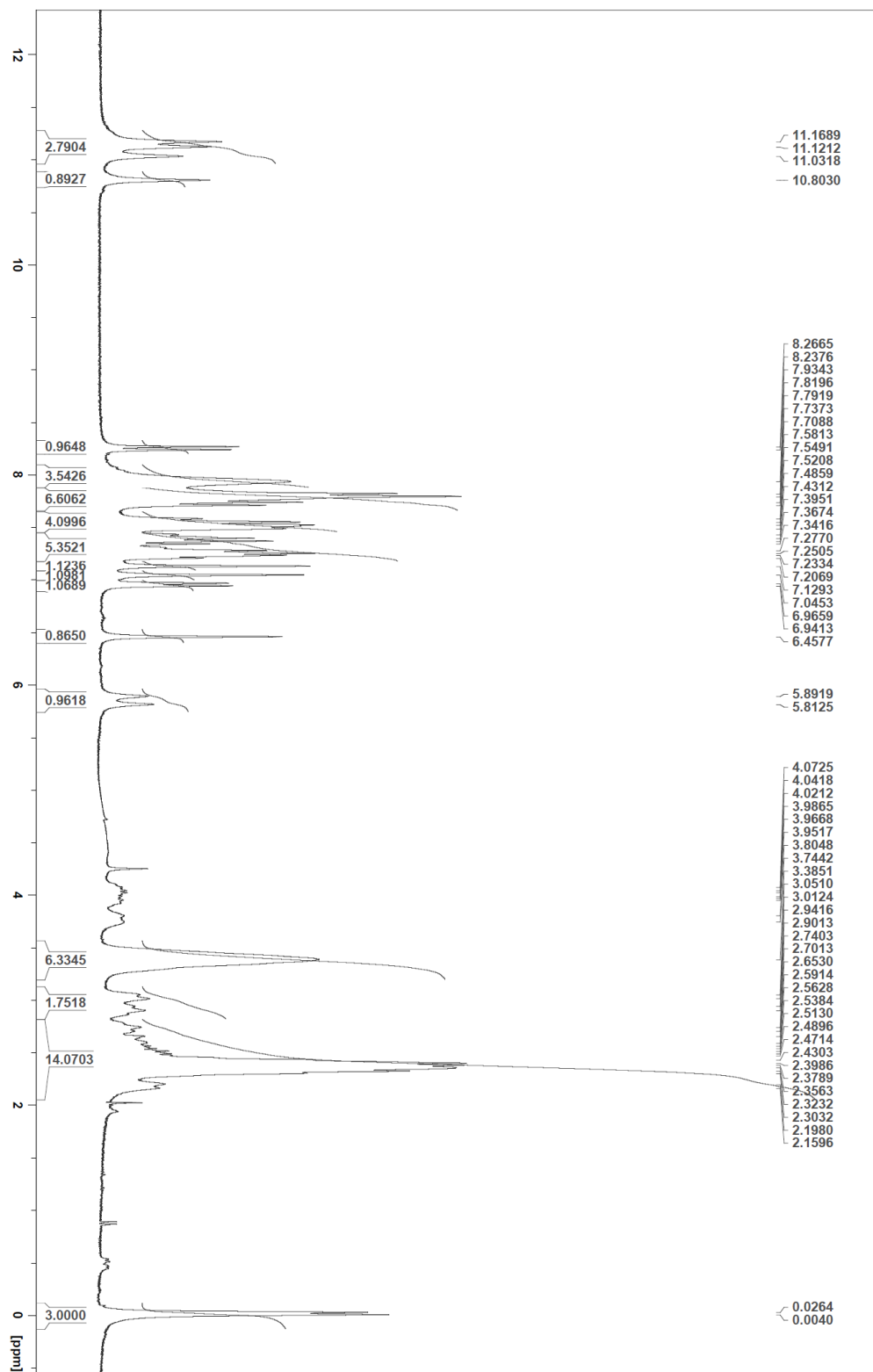


Compound 10

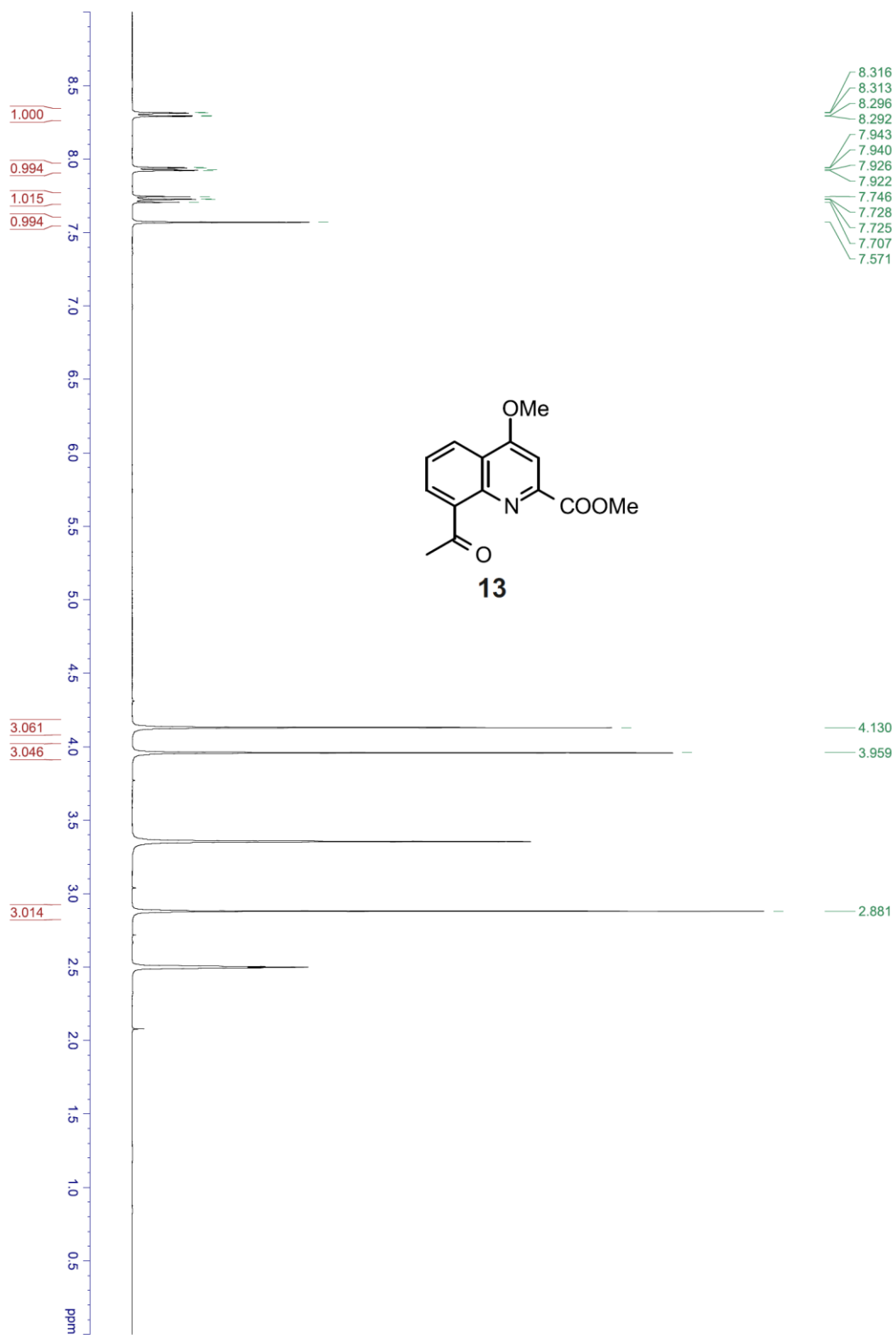


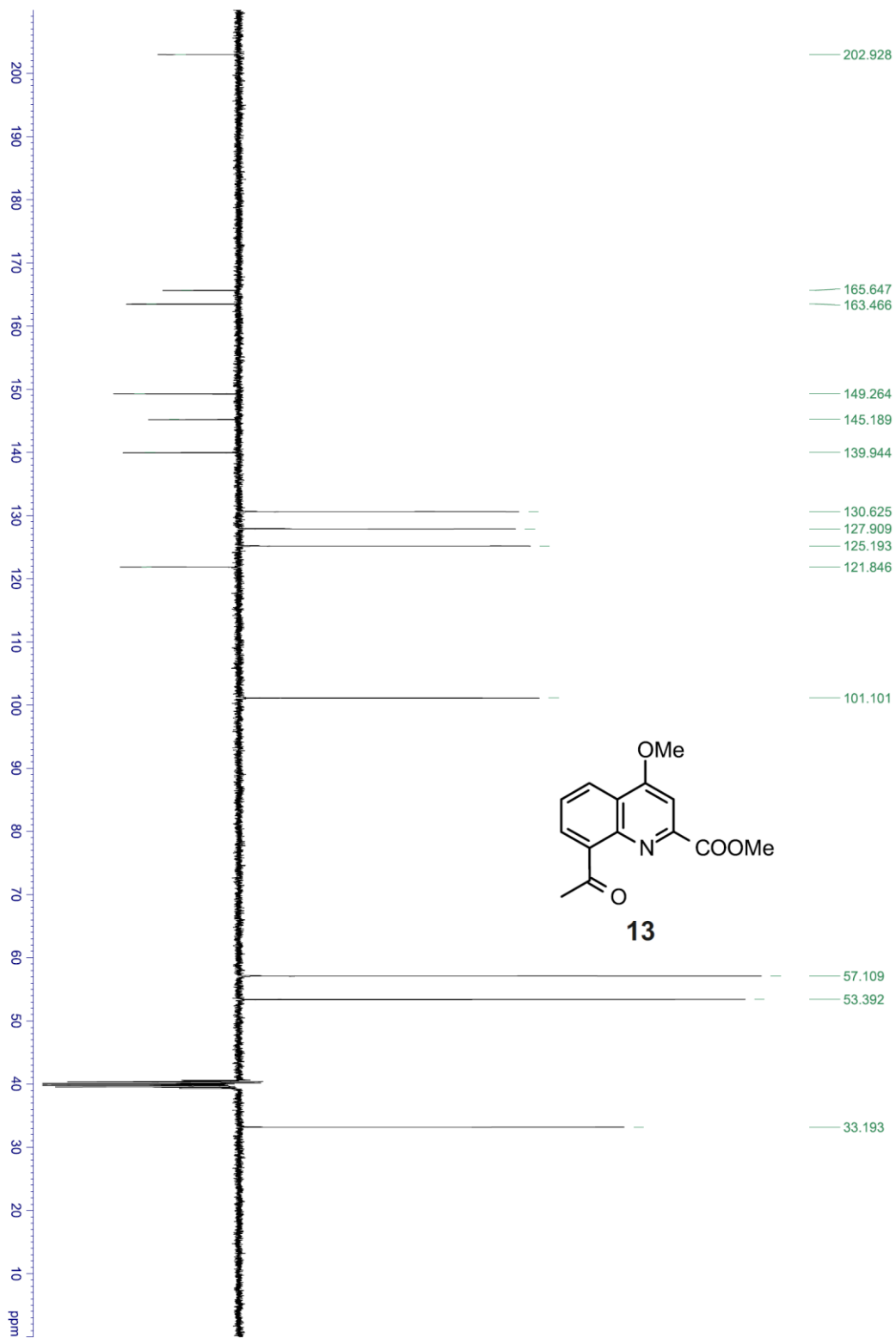


Compound 11

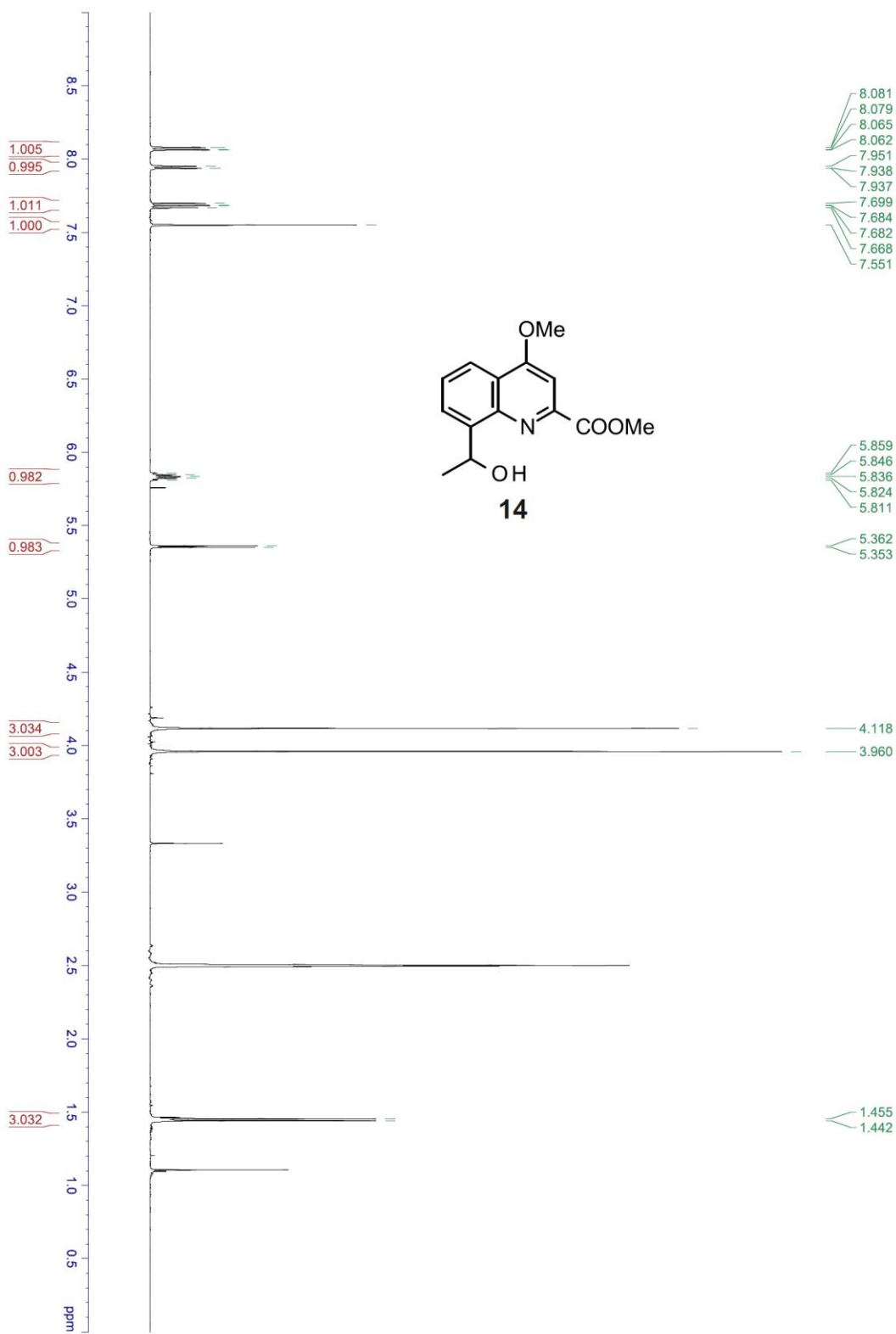


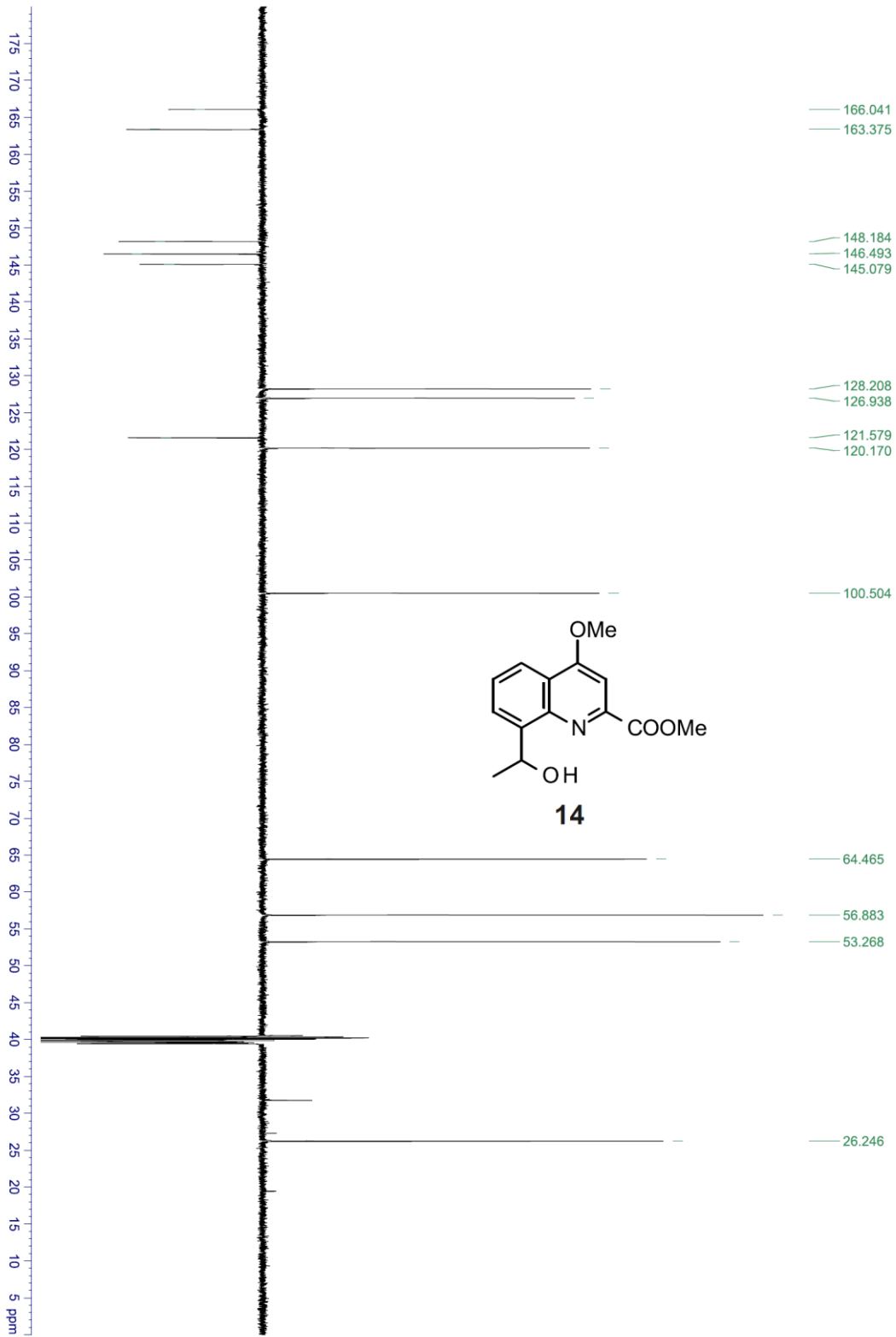
Compound 13



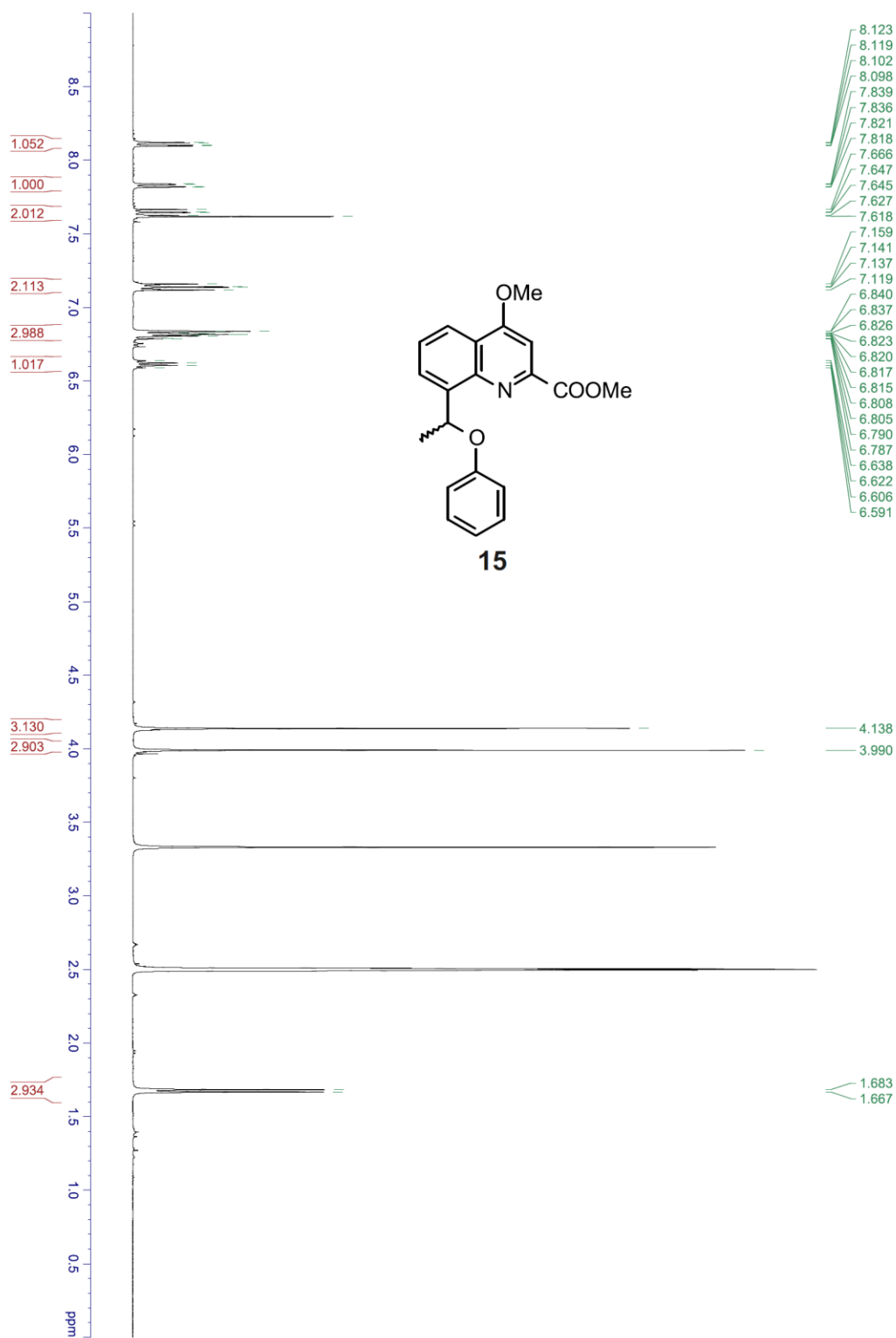


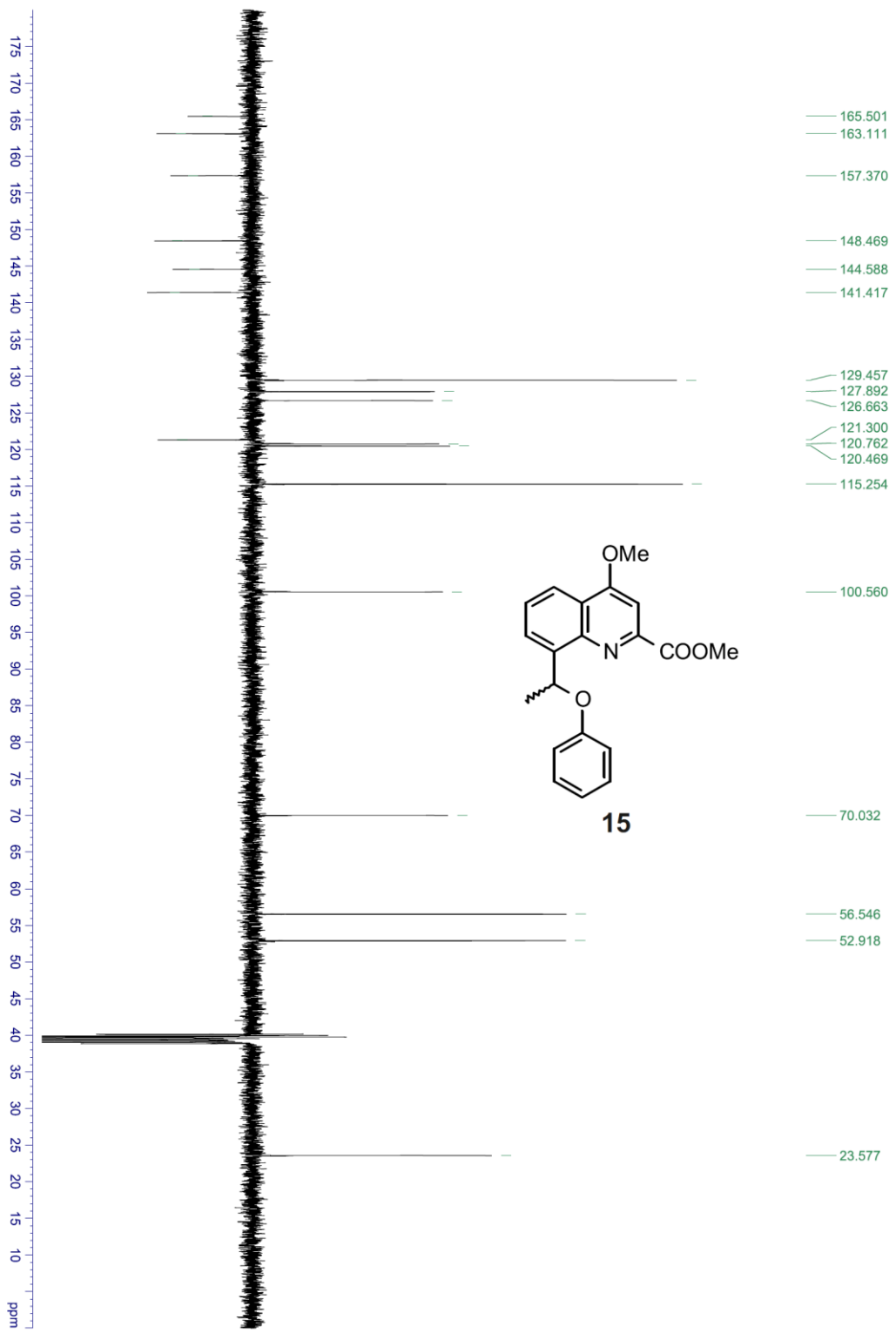
Compound 14



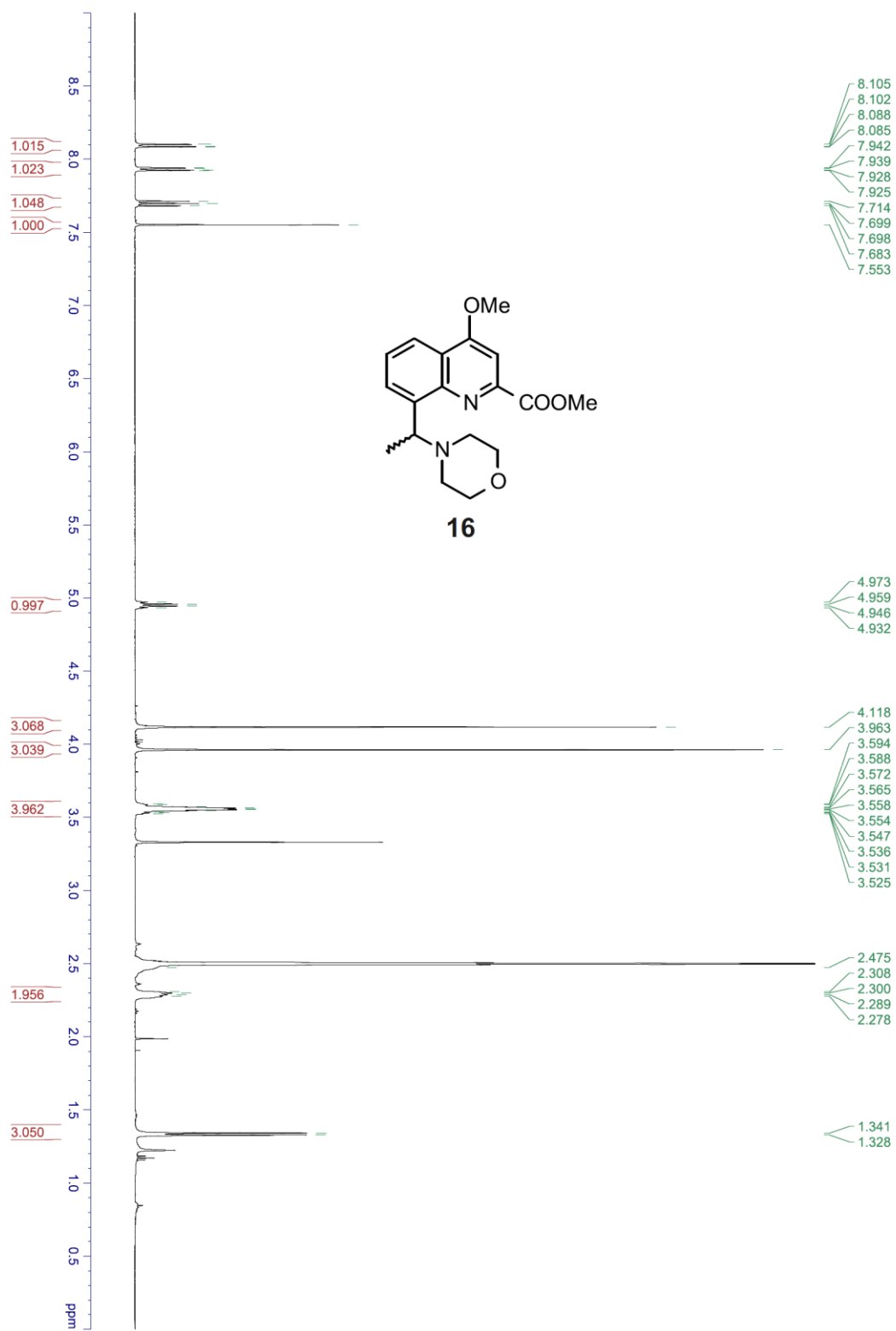


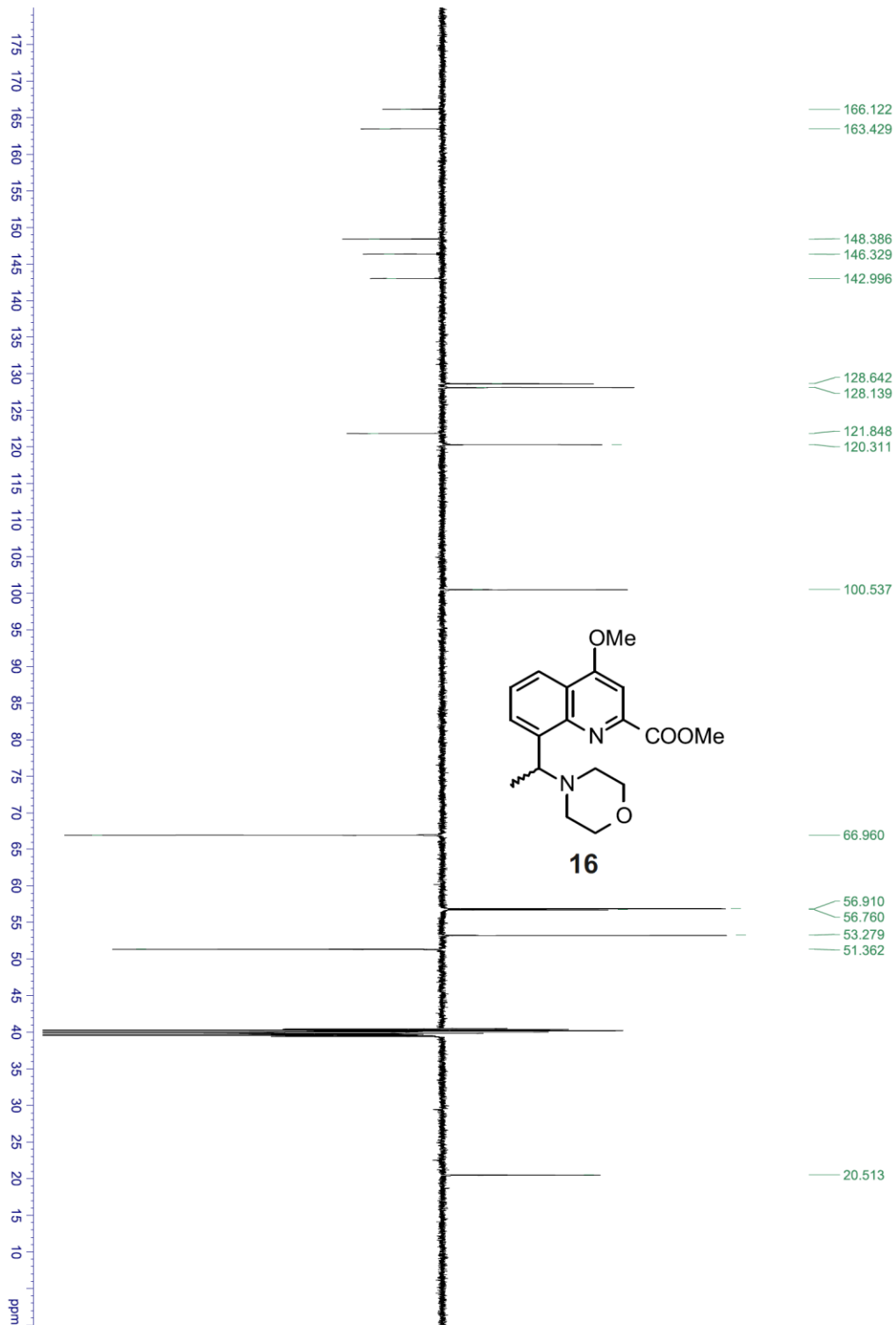
Compound 15



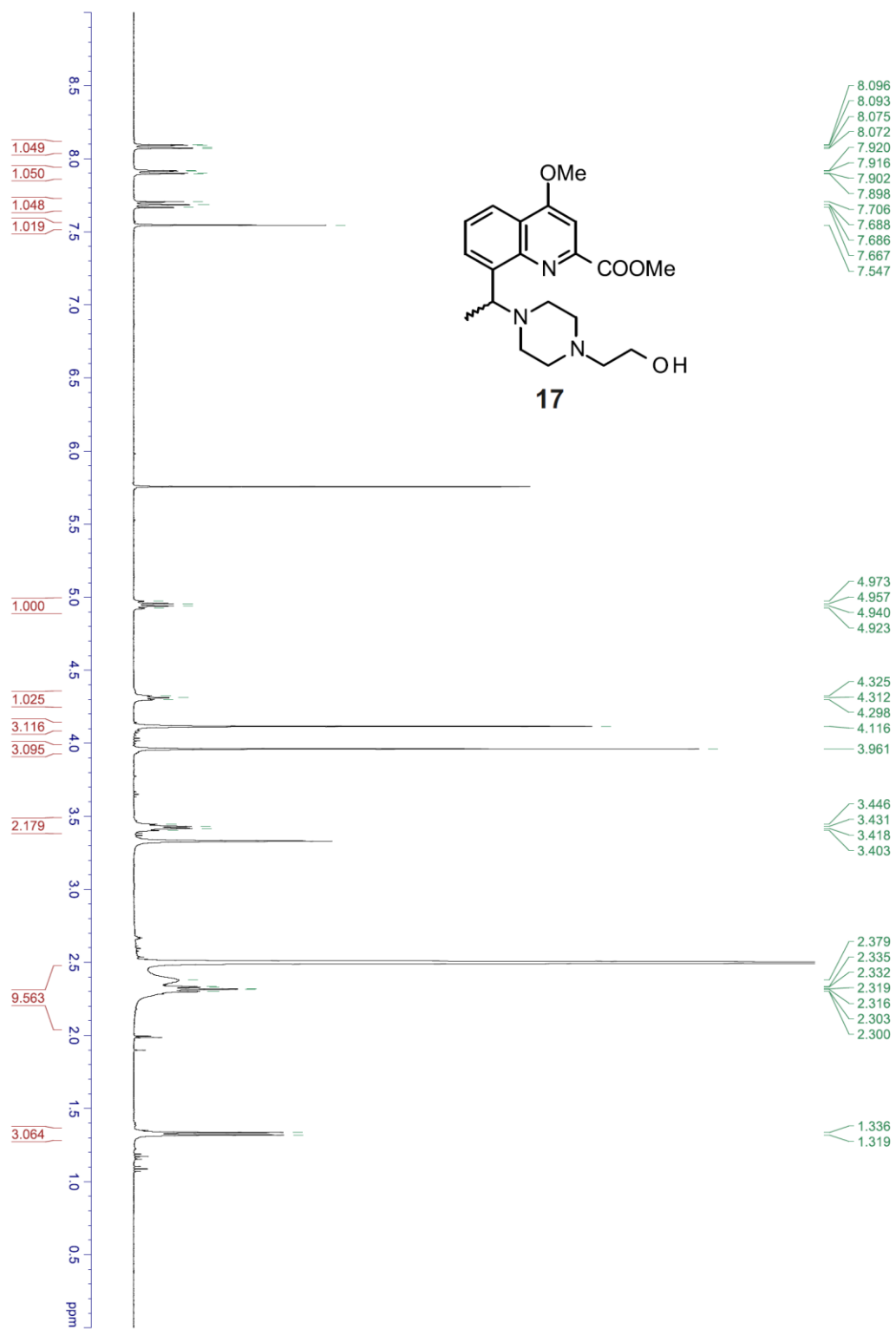


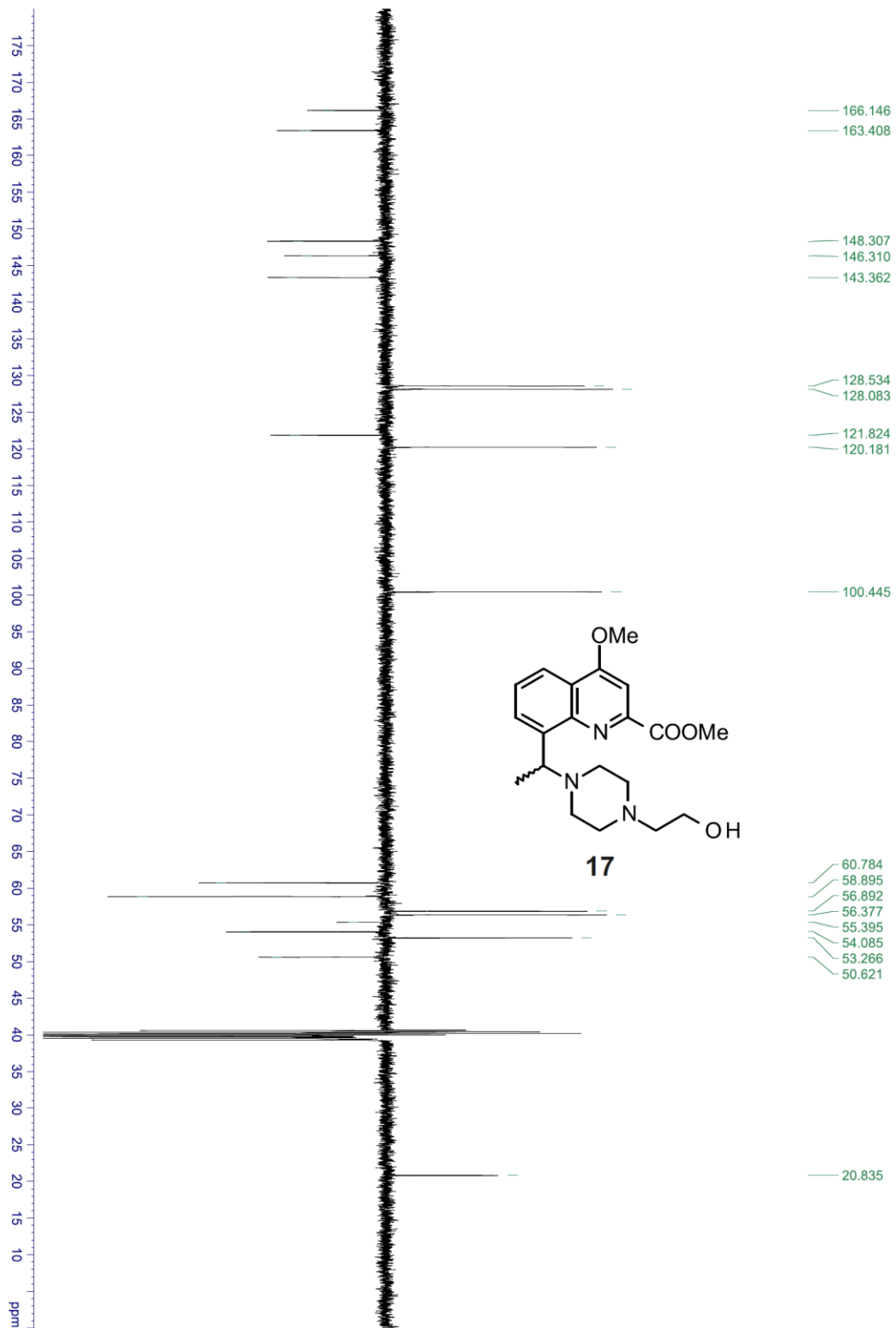
Compound 16



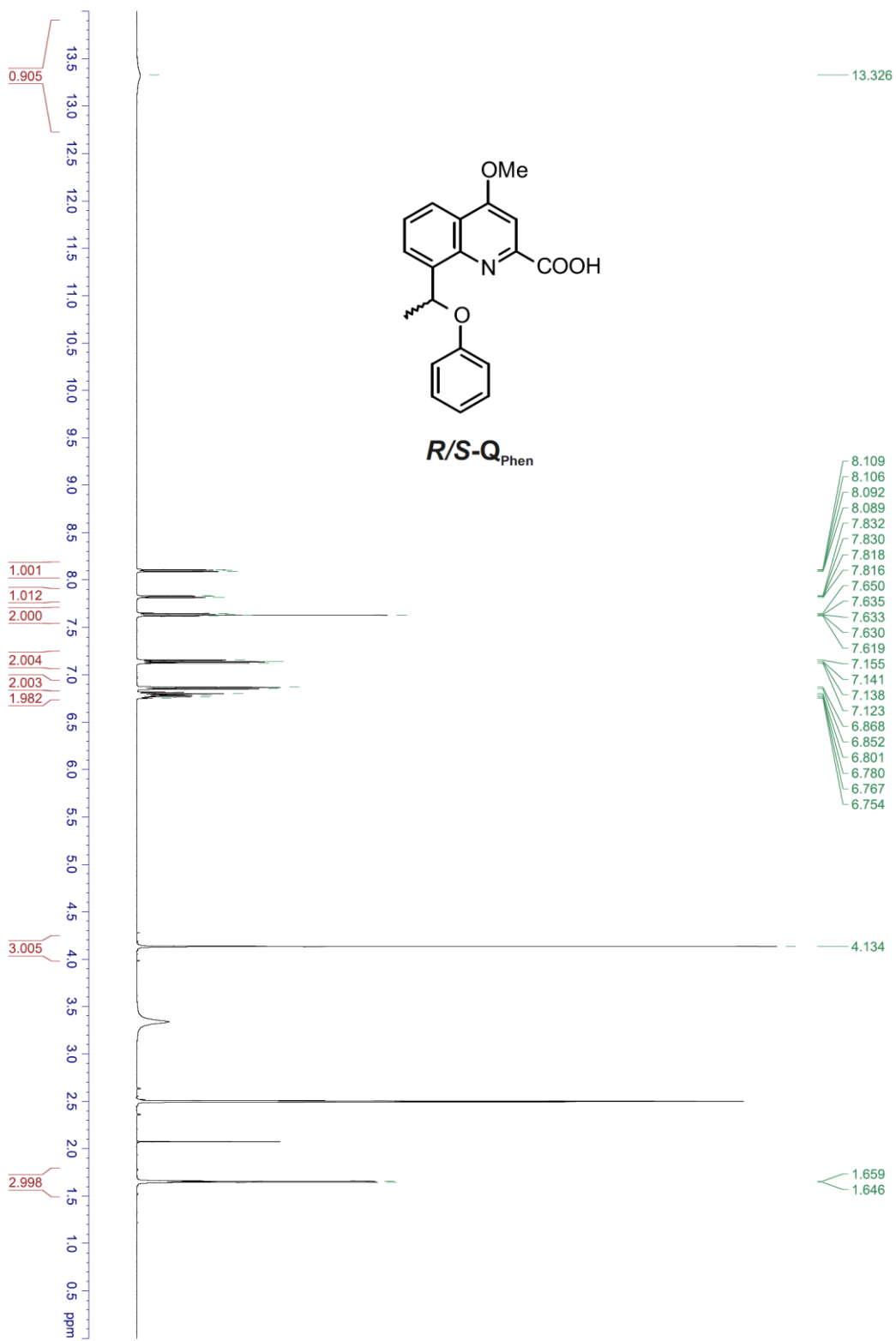


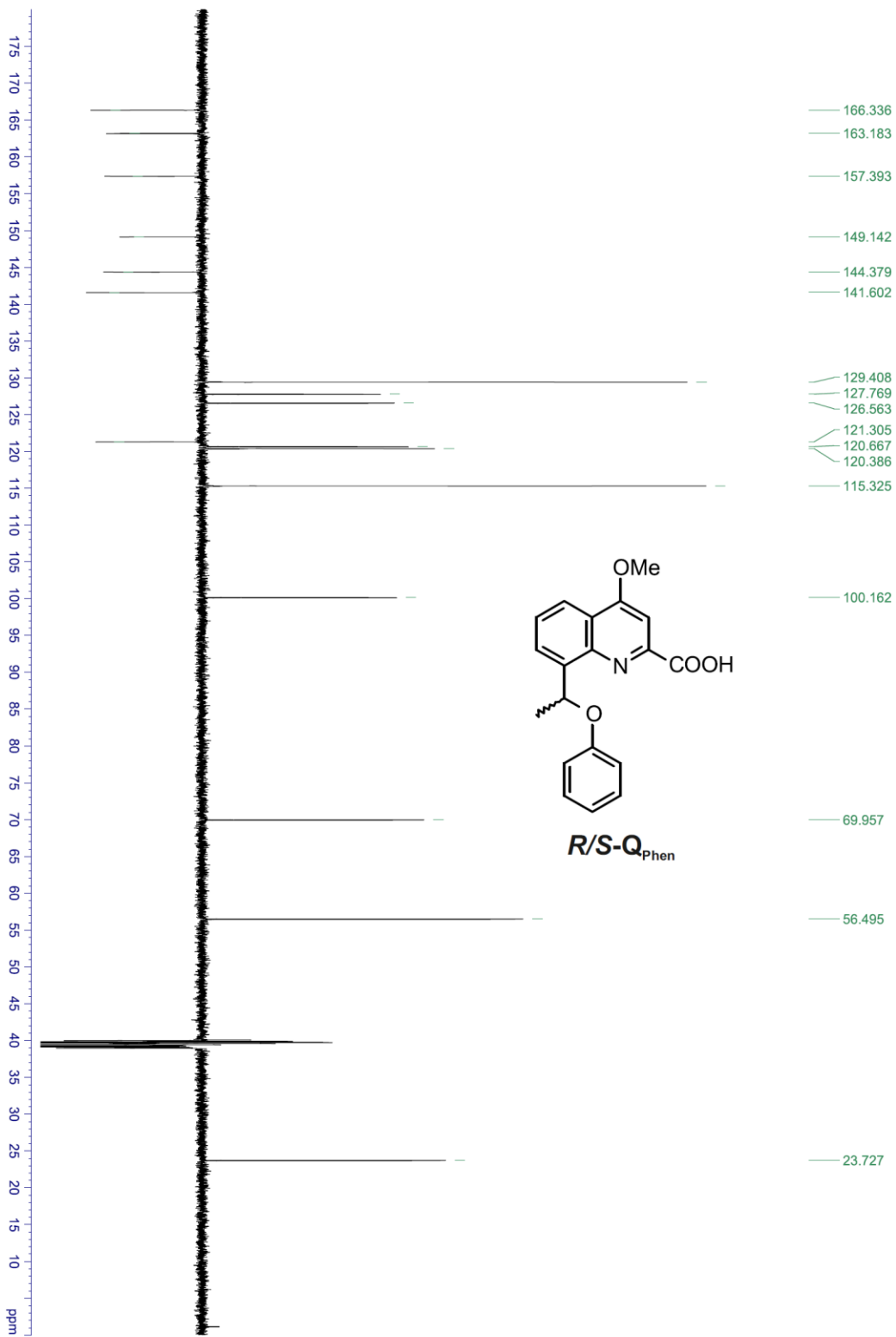
Compound 17



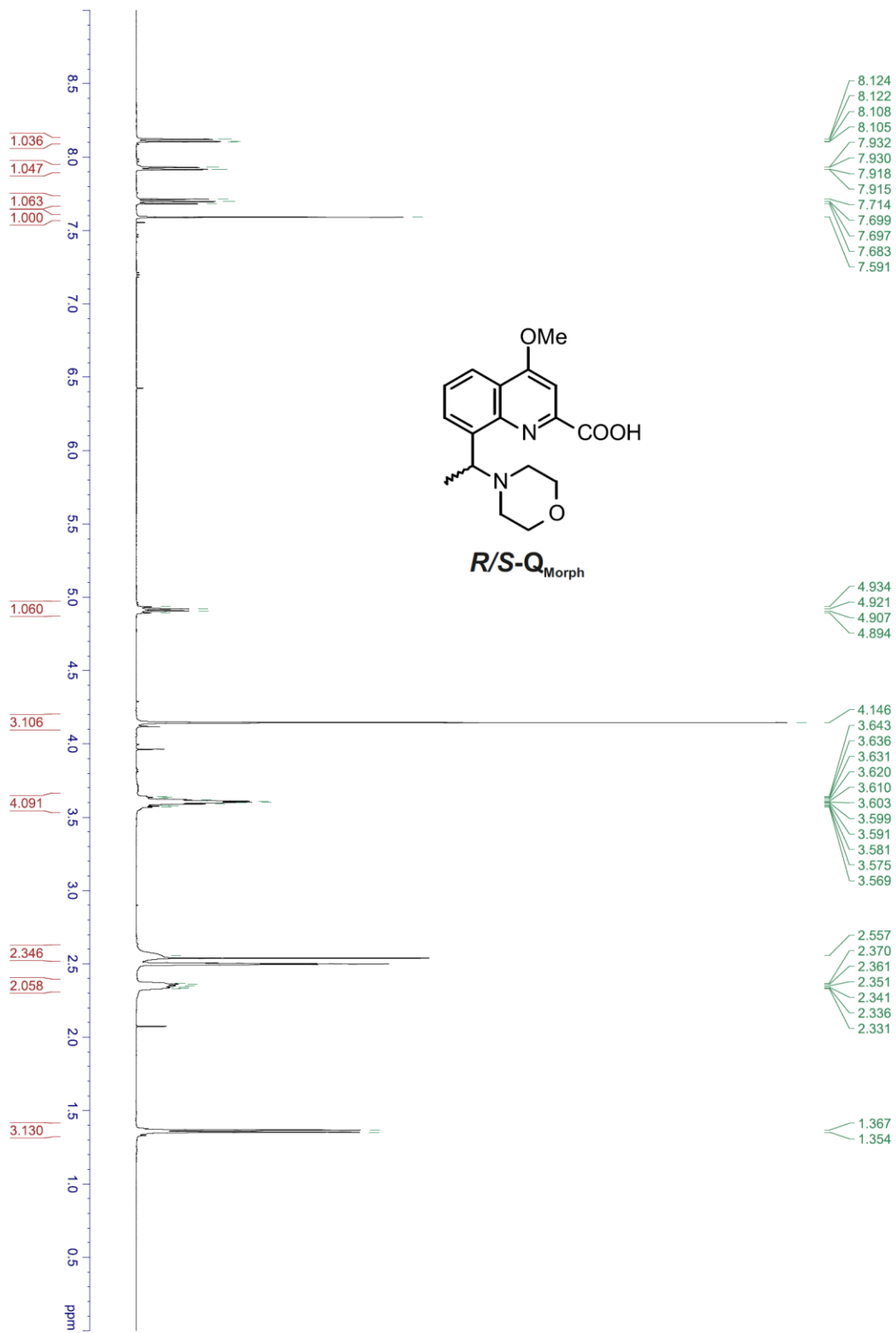


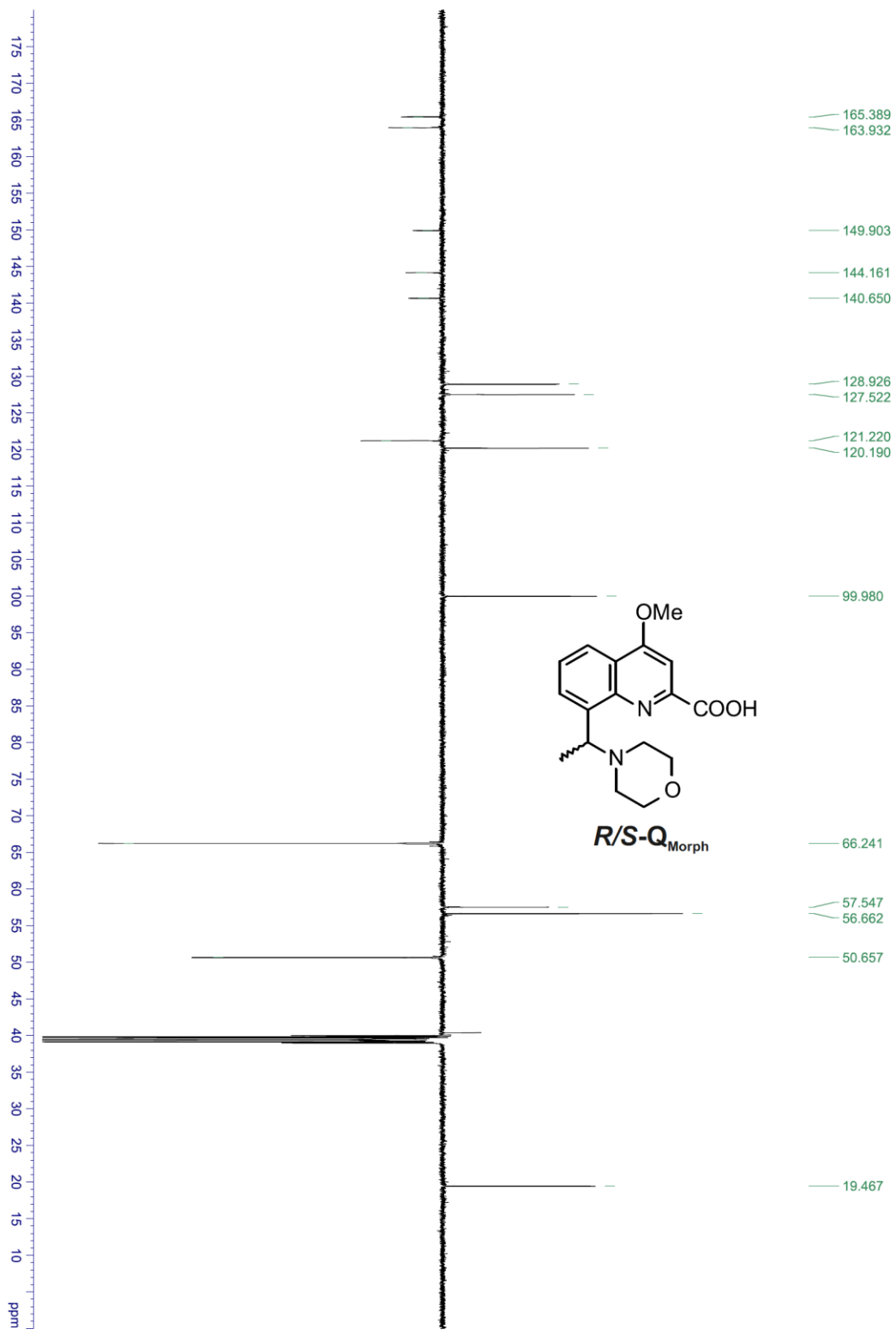
*R/S-Q*Phen

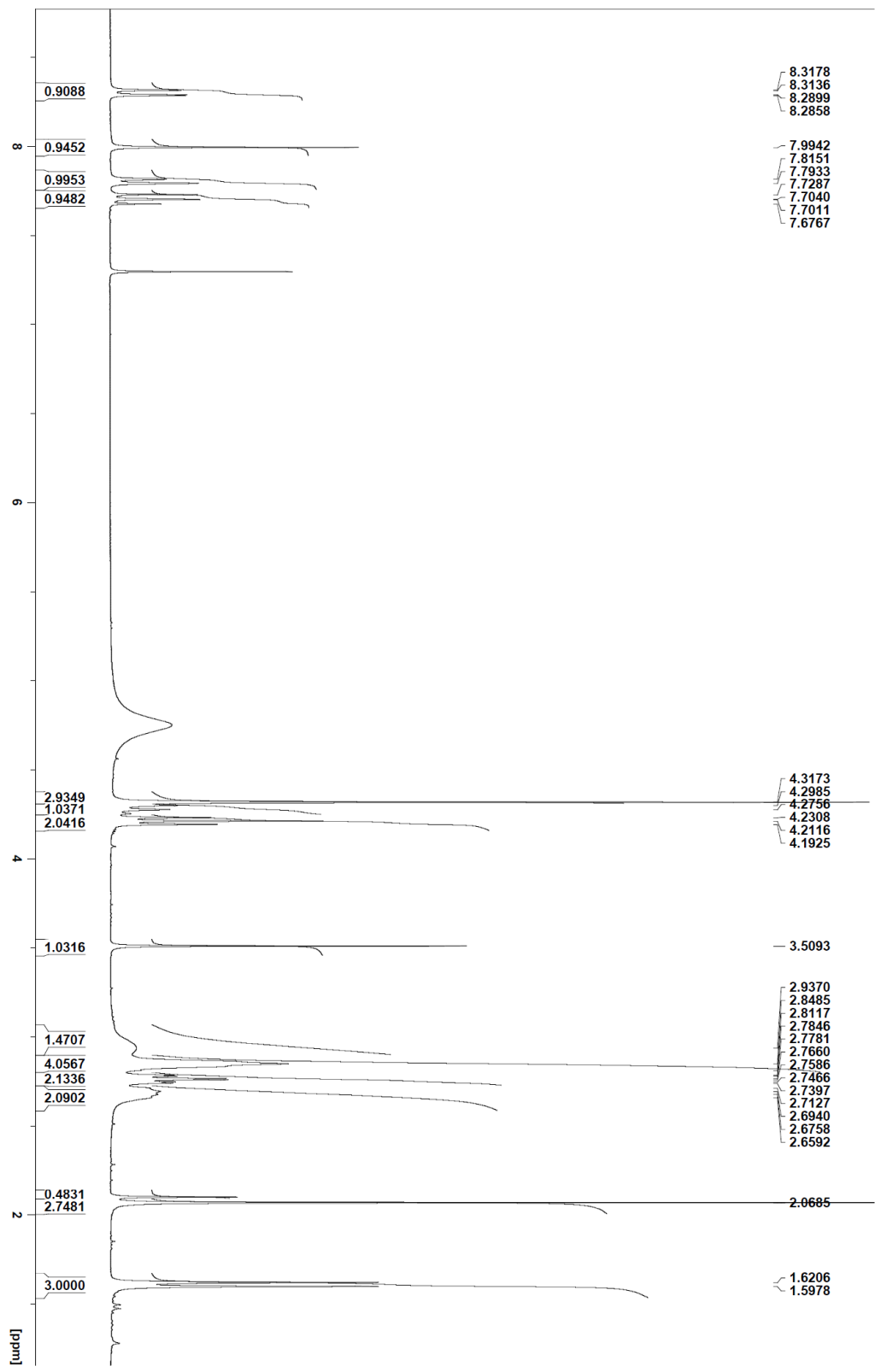


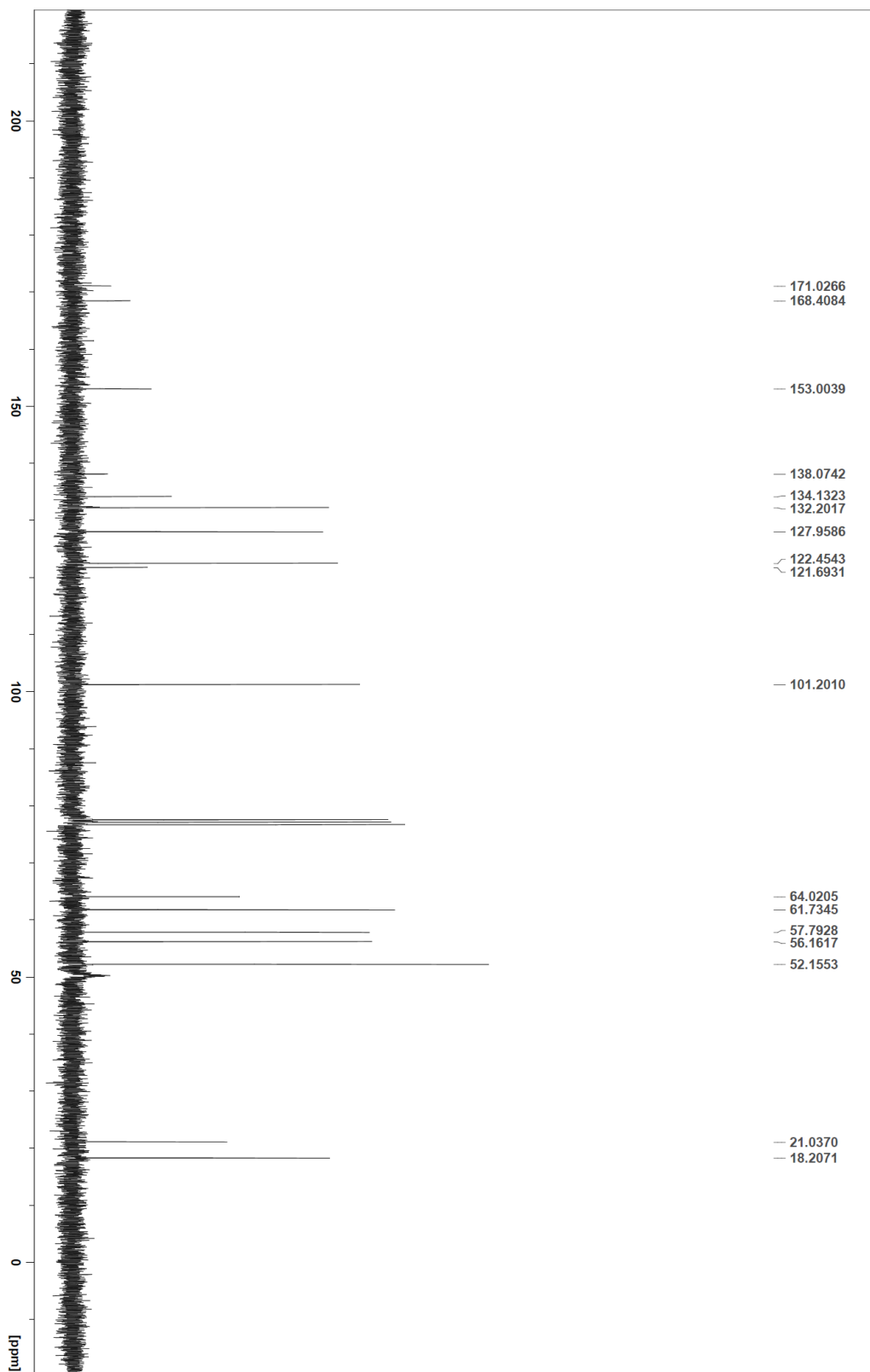


*R/S-Q*_{Morph}









S7 References

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- [2] *CrystalClear* (Version 2.1). MSC, The Woodlands, Texas, USA.
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